

COMBINATIONS OF CORTICOTROPIN RELEASING FACTOR ANTAGONISTS
AND GROWTH HORMONE SECRETAGOGUES

5 CROSS REFERENCE TO RELATED APPLICATION

This application claims priority of U.S. provisional application number 60/196,698, filed April 13, 2000.

BACKGROUND OF THE INVENTION

10 This invention relates to pharmaceutical compositions comprising combinations of corticotropin releasing factor (CRF) antagonists and growth hormone or growth hormone secretagogues, prodrugs thereof, and pharmaceutically acceptable salts of said compounds and said prodrugs. These compositions have utility, *inter alia*, in the treatment of osteoporosis or frailty associated with aging or obesity, in the treatment of cardiovascular or heart related diseases including
15 hypertension, tachycardia, and in particular congestive heart failure, as well as in accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing or accelerating the recovery of burn patients or of patients having undergone major surgery. These utilities are most relevant to mammals, and
20 particularly to humans. Accordingly, this invention also relates to methods of using such compositions for the treatment of the above diseases in mammals, particularly humans.

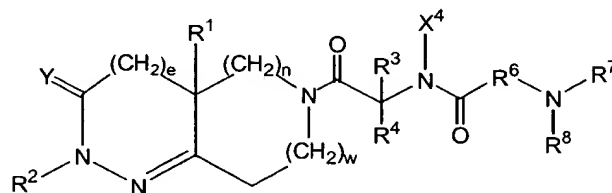
CRF antagonists are disclosed in U.S. Patents 4,605,642 and 5,063,245. Other CRF antagonists are disclosed in International patent publications WO
25 95/33750; WO 95/34563; WO 94/13661; WO 94/13644; WO 94/13643; WO 94/13676; WO 94/13677; WO 95/33727; WO 98/05661; WO 98/08847; WO 98/08846; and European patent publications EP 778277 and EP 773023. Yet other CRF antagonists are disclosed in the following patent publications: EP 576350; EP 659747; EP 812831; WO 95/10506; WO 96/35689; WO 96/39400; WO 97/00868;
30 WO 97/14684; WO 97/29109; WO 97/29110; WO 97/35539; WO 97/35580; WO 97/35846; WO 97/44038; WO 97/45421; WO 98/03510; WO 98/08821; WO 98/11075; WO 98/15543; WO 98/21200; WO 98/27066; WO 98/29397; WO 98/29413; WO 98/42699; WO 98/35967; WO 98/42706; WO 98/45295; WO 98/47874; WO 98/47903; WO 98/51312; WO 99/01454; WO 99/01439; WO
35 99/10350; WO 99/12908; WO 99/00373; WO 99/38868; WO 99/51597; WO

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99/51599; WO 99/40089; WO 99/51598; and WO 99/51600. Still more CRF antagonists are disclosed in United States Patents 5,109,111; 5,132,111; 5,245,009; 5,464,847; 5,493,006; 5,510,458; 5,644,057; 5,663,292; 5,668,145; 5,705,646; 5,712,303; and 5,723,608. An overview of the patent literature on CRF antagonists is provided in T.E. Christos and A. Arvanitis, Exp. Opin. Ther. Patents (1998) 8(2):143-152. Many of the above cited publications include information on how to make the CRF antagonists described therein.

The importance of CRF antagonists is set out in the literature, e.g., P. Black, Scientific American: "Science & Medicine," 1995, 2:16-25; T. Lovenberg, et al., Current Pharmaceutical Design, 1995, 1: 305-316; D.T. Chalmers et al., Trends in Pharmacological Sciences, April 1996, pages 166-172; and United States Patent 5,063,245. An outline of the activities possessed by CRF antagonists is found in M. J. Owens et al., 1991, Pharm. Rev., 43:425-473. CRF antagonists are described in the art as being effective in the treatment of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthemia, bipolar disorders, and cyclothymia; chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; pain perception such as fibromyalgia; headache; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhea; post-operative ileus; colonic hypersensitivity; irritable bowel syndrome; Crohn's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension, congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, Parkinson's disease, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; infertility; cancer; muscular spasms; urinary incontinence; hypoglycemia and immune dysfunctions including stress induced immune dysfunctions, immune suppression and human immunodeficiency virus infections; and stress-induced infections in humans and animals.

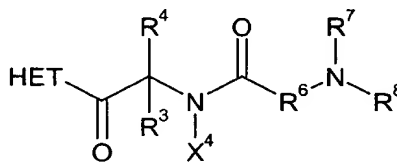
PCT publication WO 97/24369, which is incorporated herein by reference, discloses growth hormone secretagogues of formula III:



III

wherein the variables are as defined in WO 97/24369.

- 5 PCT publication WO 98/58947, which is incorporated herein by reference, discloses growth hormone secretagogues of formula IV:



IV

wherein the variables are as defined in WO 98/58947.

- 10 Other growth hormones and growth hormone secretagogues that can be used to treat the disorders recited in the methods and compositions of this invention are referred to in PCT international patent application numbers PCT/US97/07516 (published as WO 97/41879) and PCT/DK98/00249 (published as WO 98/58950), as well as in United States patents 5,206,235; 5,283,241; and 5,492,916. Many of the
15 above-cited publications disclose how to make or obtain the growth hormone or growth hormone secretagogue described therein. All of the above-cited patent applications and United States patents are incorporated herein by reference in their entirety. Any growth hormone and growth hormone secretagogue, either presently known or yet to be discovered, may be used in the present invention.

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SUMMARY

- This invention is directed to pharmaceutical compositions comprising a CRF antagonist, a growth hormone secretagogue or growth hormone, and preferably
25 additionally a pharmaceutically acceptable carrier, vehicle, or diluent.

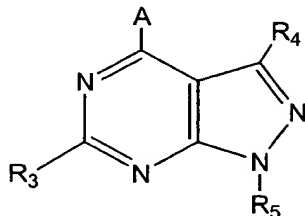
This invention is also directed to methods for treating or preventing osteoporosis or frailty associated with aging or obesity, cardiovascular or heart related disease, in particular hypertension, tachycardia, and congestive heart failure, accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or of patients having undergone major surgery, wherein said methods comprise administering to a human or other mammal an amount of a pharmaceutical composition as defined herein, which is effective in treating or preventing the stated disease or condition. This invention is also directed to methods for treating or preventing the diseases or conditions described herein by the co-administration of two separate pharmaceutical compositions. In this latter embodiment, a first composition comprises a CRF antagonist, and a second composition comprises a growth hormone or growth hormone secretagogue. These first and second compositions are preferably co-administered either simultaneously, or in a specifically timed manner.

This invention is also directed to kits comprising a) an amount of a CRF antagonist, in a first unit dosage form; b) an amount of a growth hormone secretagogue or growth hormone in a second unit dosage form; and c) a container.

This invention is also directed to kits comprising a) a pharmaceutical composition comprising an amount of a growth hormone or growth hormone secretagogue, b) a package containing the above composition, and c) a package insert (which may be integral with the package), wherein it is stated on the package insert that the pharmaceutical composition is to be administered simultaneously or in a specifically timed manner with a separate pharmaceutical composition containing at least one CRF antagonist.

This invention is also directed to kits, comprising a) a pharmaceutical composition comprising an amount of a CRF antagonist, b) a package containing the above composition, and c) a package insert that may be integral with the package, wherein it is stated on the package insert that the pharmaceutical composition is to be administered simultaneously or in a specifically timed manner with a pharmaceutical composition containing at least one growth hormone or growth hormone secretagogue.

A group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



5 or a pharmaceutically acceptable acid addition salt thereof, wherein

A is NR_1R_2 , $\text{CR}_1\text{R}_2\text{R}_{11}$, or $\text{C}(=\text{CR}_1\text{R}_{12})\text{R}_2$, $\text{NHCR}_1\text{R}_2\text{R}_{11}$, $\text{OCR}_1\text{R}_2\text{R}_{11}$, $\text{SCR}_1\text{R}_2\text{R}_{11}$, NHNHR_1R_2 , $\text{CR}_2\text{R}_{11}\text{NHR}_1$, $\text{CR}_2\text{R}_{11}\text{OR}_1$, $\text{CR}_2\text{R}_{11}\text{SR}_1$ or $\text{C}(\text{O})\text{R}_2$;

10 R_1 is hydrogen, or C_1 - C_6 alkyl which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_6 alkoxy, $\text{O}-\text{C}(\text{O})-(\text{C}_1-\text{C}_6 \text{ alkyl})$, $\text{O}-\text{C}(\text{O})-\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$; amino, $\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{S}(\text{C}_1-\text{C}_6 \text{ alkyl})$, $\text{OC}(\text{O})\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{N}(\text{C}_1-\text{C}_2 \text{ alkyl})\text{C}(\text{O})(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_1-\text{C}_4 \text{ alkyl})$, COOH , $\text{CO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{C}(\text{O})\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, SH , CN , NO_2 , $\text{SO}(\text{C}_1-\text{C}_4 \text{ alkyl})$; $\text{SO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{SO}_2\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{SO}_2\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, and said C_1 - C_6 alkyl may
15 have one or two double or triple bonds;

R_2 is C_1 - C_{12} alkyl, aryl or $(\text{C}_1-\text{C}_{10} \text{ alkylene})\text{aryl}$ wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl,
20 azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or $(\text{C}_1-\text{C}_6 \text{ alkylene})\text{cycloalkyl}$, wherein said cycloalkyl may have one or two of O, S or N-Z, wherein Z is hydrogen, substituted, independently, for one or two carbons of said cycloalkyl, C_1 - C_4 alkyl, benzyl or C_1 - C_4 alkanoyl, wherein R^2 may be substituted independently by
25 C_6 alkoxy, $\text{OC}(\text{O})(\text{C}_1-\text{C}_6 \text{ alkyl})$, $\text{O}-\text{C}-\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, $\text{S}(\text{C}_1-\text{C}_6 \text{ alkyl})$, NH_2 , $\text{NH}(\text{C}_1-\text{C}_2 \text{ alkyl})$, $\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})\text{C}(\text{O})(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{NHC}(\text{O})(\text{C}_1-\text{C}_4 \text{ alkyl})$, COOH , $\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{C}(\text{O})\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, SH , CN , NO_2 , $\text{SO}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{SO}_2(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{SO}_2\text{NH}(\text{C}_1-\text{C}_4 \text{ alkyl})$, $\text{SO}_2\text{N}(\text{C}_1-\text{C}_4 \text{ alkyl})(\text{C}_1-\text{C}_2 \text{ alkyl})$, and wherein said C_1 - C_{12} alkyl or C_1 - C_{10} alkylene may have one to three double
30 or triple bonds; or

NR₁R₂ or CR₁R₂R₁₁ may form a 4- to 8-membered ring optionally having one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C₁-C₄ alkyl, benzyl, or C₁-C₄ alkanoyl;

5 R₃ is hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C₁-C₆ alkyl), NH(C₁-C₆ alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SH, S(C₁-C₄ alkyl), SO(C₁-C₄ alkyl), or SO₂(C₁-C₄ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may have one or two double or triple bonds and may be substituted by from 1 to 3 R₇ substituents independently selected from the group consisting of hydroxy, amino, C₁-C₃ alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NHC(O)CH₃, fluoro, chloro or
10 C₁-C₃ thioalkyl;

R₄ is hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, C₁-C₆ alkoxy, amino, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₂ alkyl), SO_n(C₁-C₆ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C₁-C₆ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(O)(C₁-C₄ alkyl), NH(C₁-C₄
15 alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl), C(O)O(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, or tetrazolyl, wherein each one of the above
20 groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C₁-C₆ alkyl, C₁-C₆ alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C₁-C₄ alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl),
25 COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂, NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R₅ is not unsubstituted phenyl;

30 R₁₁ is hydrogen, hydroxy, fluoro, chloro, COO(C₁-C₂ alkyl), cyano, or CO(C₁-C₂ alkyl); and

R₁₂ is hydrogen or C₁-C₄ alkyl;

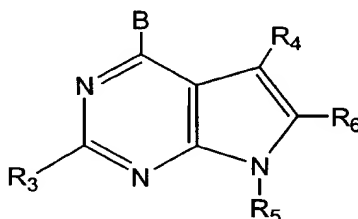
with the provisos that:

(a) A is not straight chain C₁-C₁₂ alkyl;

(b) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxy-ribofuranosyl; and

(c) when R^5 is phenyl, said phenyl is substituted by two or three substituents.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



or a pharmaceutically acceptable acid addition salt thereof, wherein

B is NR_1R_2 , $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1 - C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_8 alkoxy, $O-C(=O)-(C_1-C_6 \text{ alkyl})$, $O-C(=O)NH(C_1-C_4 \text{ alkyl})$, $O-C(=O)-N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, amino, $NH(C_1-C_4 \text{ alkyl})$, $N(C_1-C_2 \text{ alkyl})(C_1-C_4 \text{ alkyl})$, $S(C_1-C_6 \text{ alkyl})$, $N(C_1-C_4 \text{ alkyl})C(=O)(C_1-C_4 \text{ alkyl})$, $NH(C_1-C_4 \text{ alkyl})$, $COOH$, $C(=O)O(C_1-C_4 \text{ alkyl})$, $C(=O)NH(C_1-C_4 \text{ alkyl})$, $C(=O)N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, SH , CN , NO_2 , $SO(C_1-C_4 \text{ alkyl})$, $SO_2(C_1-C_4 \text{ alkyl})$, $SO_2NH(C_1-C_4 \text{ alkyl})$, $SO_2N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, and said C_1 - C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1 - C_{12} alkyl, aryl or $(C_1$ - C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or $(C_1$ - C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1 - C_4 alkyl, benzyl or C_1 - C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1 - C_4 alkyl, or one of hydroxy, bromo, iodo, C_1 - C_6 alkoxy, $O-C(=O)-(C_1-C_6 \text{ alkyl})$, $O-C-N(C_1-C_4 \text{ alkyl})(C_1-$

C₂ alkyl), S(C₁-C₆ alkyl), NH₂, NH(C₁-C₂ alkyl), N(C₁-C₂ alkyl) (C₁-C₄ alkyl), N(C₁-C₄)-C(=O)(C₁-C₄ alkyl), NHC(=O)(C₁-C₄), COOH, C(=O)O(C₁-C₄ alkyl), C(=O)NH(C₁-C₄ alkyl), C(=O)N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SH, CN, NO₂, SO(C₁-C₄ alkyl), SO₂(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), and wherein said C₁-C₁₂

5 alkyl or C₁-C₁₀ alkylene may contain one to three double or triple bonds; or

NR₁R₂ or CR₁R₂R₁₁ may form a saturated 3- to 8 membered carbocyclic ring of which the 5- to 8-membered ring contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C₁-C₄ alkyl, benzyl or C₁-C₄ alkanoyl;

R₃ is hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C₁-C₆ alkyl), NH(C₁-C₆ alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SH, S(C₁-C₄ alkyl), SO(C₁-C₄ alkyl), or SO₂(C₁-C₄ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may contain from one or two double or triple bonds and may be substituted by from 1 to 3 substituents R₈ independently selected from the group consisting of hydroxy, amino, C₁-C₃ alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NHCH₃, fluoro, chloro or C₁-C₃ thioalkyl;

R₄ and R₆ are each independently hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, C₁-C₆ alkoxy, amino, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)(C₁-C₂ alkyl), SO_n(C₁-C₆ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C₁-C₆ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(=O)(C₁-C₄ alkyl), NH(C₁-C₄ alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl), C(=O)O(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

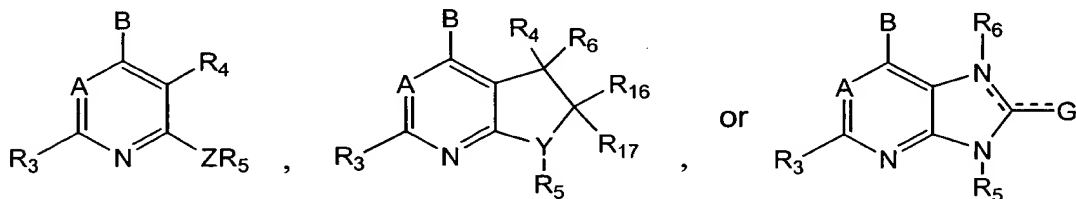
R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to four of fluoro, chloro, C₁-C₆ alkyl, C₁-C₆ alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, NH(C₁-C₄ alkyl), N(C₁-C₄)(C₁-C₂ alkyl), COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂, NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may

be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R₅ is not unsubstituted phenyl;

R₁₁ is hydrogen, hydroxy, fluoro, chloro, COO(C₁-C₂ alkyl), cyano, or CO(C₁-C₂ alkyl); and

- 5 R₁₂ is hydrogen or C₁-C₄ alkyl; with the proviso that (1) when R₅ is 4-bromophenyl, R₃ is hydrogen, and R₄ and R₆ are methyl, then B is not methylamino or ethyl, and (2) when R₅ is 4-bromophenyl, and R₃, R₄ and R₆ are methyl, then B is not 2-hydroxyethylamino.

- 10 Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



or a pharmaceutically acceptable acid addition salt thereof, wherein

- 15 A is CR₇ or N;
 B is NR₁R₂, CR₁R₂R₁₁, C(=CR₂R₁₂)R₁, NHCHR₁R₂, OCHR₁R₂, SCHR₁R₂, CHR₂OR₁₂, CHR₂SR₁₂, C(S)R₂ or C(O)R₂;
 G is oxygen, sulfur, NH, NH₃, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH₂, NHCH₃, N(CH₃)₂ or trifluoromethyl;
 20 Y is CH or N;
 Z is NH, O, S, N (C₁-C₂ alkyl), or CR₁₃R₁₄, wherein R₁₃ and R₁₄ are each independently hydrogen, trifluoromethyl, or C₁-C₄ alkyl, or one of R₁₃ and R₁₄ may be cyano, chloro, bromo, iodo, fluoro, hydroxy, O(C₁-C₂ alkyl), amino, NH(C₁-C₂ alkyl), or CR₁₃R₁₄ may be C=O or cyclopropyl;
 25 R₁ is C₁-C₆ alkyl which may be substituted by one or two substituents R₈ independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, O-CO-(C₁-C₄ alkyl), O-CO-NH(C₁-C₄ alkyl), O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), NH(C₁-C₄ alkyl), N(C₁-C₂ alkyl)(C₁-C₄ alkyl), S(C₁-C₄ alkyl), N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), NHCO(C₁-C₄ alkyl), COO(C₁-C₄ alkyl), CONH(C₁-C₄ alkyl),

CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), S(C₁-C₄ alkyl), CN, NO₂, SO(C₁-C₄ alkyl), SO₂(C₁-C₄ alkyl), and said C₁-C₆ alkyl or C₁-C₄ alkyl may contain one double or triple bond;

R₂ is C₁-C₁₂ alkyl, aryl or (C₁-C₄ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C₁-C₆ alkylene)cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-R₉ wherein R₉ is hydrogen, or C₁-C₄ alkyl, wherein the above defined R₂ may be substituted independently by from one to three of chloro, fluoro, or C₁-C₄ alkyl, or one of bromo, iodo, C₁-C₆ alkoxy, O-CO-(C₁-C₆ alkyl), O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), S(C₁-C₆ alkyl), CN, NO₂, SO(C₁-C₄ alkyl), or SO₂(C₁-C₄ alkyl), and wherein said C₁-C₁₂ alkyl or C₁-C₄ alkylene may contain one double or triple bond; or

NR₁R₂ or CR₁R₂R₁₁ may form a saturated 5- to 8-membered carbocyclic ring which may contain one or two double bonds or one or two of O or S;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, methylthio, methylsulfonyl, CH₂OH or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, C₁-C₄ alkoxy, amino, nitro, NH(C₁-C₄ alkyl), N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO_n(C₁-C₄ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, CO(C₁-C₄ alkyl), CHO, or COO(C₁-C₄ alkyl), wherein said C₁-C₄ alkyl may contain one or two double or triple bonds and may be substituted by one or two of hydroxy, amino, carboxy, NHCOCH₃, NH(C₁-C₂ alkyl), N(C₁-C₂ alkyl)₂, COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, C₁-C₃ thioalkyl, fluoro, chloro, cyano or nitro;

R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each one of the above groups R₅ is substituted independently by from one to three of fluoro, chloro, C₁-C₆ alkyl, or C₁-C₆ alkoxy, or one of hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, NH(C₁-C₄ alkyl), N(C₁-C₆)(C₁-C₂ alkyl), COOH, COO(C₁-C₄ alkyl), CO(C₁-C₄ alkyl), SO₂NH(C₁-C₄ alkyl), SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), SO₂NH₂, NHSO₂(C₁-C₄ alkyl), S(C₁-C₆ alkyl), or SO₂(C₁-C₆ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl may be substituted by one or two of fluoro, hydroxy, amino, methylamino, dimethylamino or acetyl;

R₆ is hydrogen, or C₁-C₆ alkyl, wherein said C₁-C₆ alkyl may be substituted by one hydroxy, methoxy, ethoxy or fluoro;

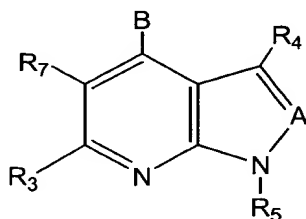
R_7 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, $O(C_1$ - C_4 alkyl), $C(O)(C_1$ - C_4 alkyl), or $C(O)O(C_1$ - C_4 alkyl), wherein the C_1 - C_4 alkyl groups may be substituted with one hydroxy, chloro or bromo, or one to three fluoro;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

5 R_{12} is hydrogen or C_1 - C_4 alkyl; and

R_{16} and R_{17} are each independently hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that they are not both methoxy or ethoxy, and CR_4R_6 and $CR_{16}R_{17}$ each independently may be $C=O$.

10 Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



or a pharmaceutically acceptable acid addition salt thereof, wherein

15 A is N or $-CR_6$;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, $-C(S)R_1$ or $-C(O)R_1$;

R_1 is C_1 - C_6 alkyl which may optionally be substituted with one or two substituents independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, $-O-CO-(C_1$ - C_4 alkyl), $-O-CO-NH(C_1$ - C_4 alkyl), $-O-CO-N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_2 alkyl)(C_1 - C_4 alkyl), $-S(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl) $CO(C_1$ - C_4 alkyl), $-NHCO(C_1$ - C_4 alkyl), $-COO(C_1$ - C_4 alkyl), $-CONH(C_1$ - C_4 alkyl), $-CON(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), CN, NO_2 , $-SO(C_1$ - C_4 alkyl), $-SO_2(C_1$ - C_4 alkyl), and wherein any of the foregoing C_1 - C_4 alkyl and C_1 - C_6 alkyl groups may optionally contain one carbon-carbon double or triple bond;

20

25

R_2 is C_1 - C_{12} alkyl, aryl, $-(C_1$ - C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, oxazolyl, or benzoxazolyl; or 3- to 8- membered cycloalkyl or $-(C_1$ - C_6

30

alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said $-(C_1-C_6 \text{ alkylene})\text{cycloalkyl}$ having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-Z wherein Z is hydrogen; or C_1-C_4 alkyl, and wherein each of said

- 5 groups R_2 may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-O-CO-(C_1-C_6 \text{ alkyl})$, $-S(C_1-C_6 \text{ alkyl})$, $-COO(C_1-C_4 \text{ alkyl})$, CN, NO_2 , $-SO(C_1-C_4 \text{ alkyl})$, and $-SO_2(C_1-C_4 \text{ alkyl})$, and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said $-(C_1-C_4 \text{ alkylene})\text{aryl}$ may
- 10 optionally contain one carbon-carbon double or triple bond;

or $-NR_1R_2$ may form a saturated 5- to 8-membered heterocyclic ring, or $-CHR_1R_2$ may form a saturated 5- to 8-membered carbocyclic ring, wherein each of these rings may optionally contain one or two carbon-carbon double bonds and wherein one or two of the carbon atoms of each of these rings may optionally be

- 15 replaced with a sulfur or oxygen atom;

R_3 is C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-CH_2OH$, $-CH_2OCH_3$, $-O(C_1-C_3 \text{ alkyl})$, $-S(C_1-C_3 \text{ alkyl})$, or $-SO_2(C_1-C_3 \text{ alkyl})$, wherein said C_1-C_3 alkyl may optionally contain one carbon-carbon double or triple bond;

- R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, amino, $-NHCH_3$, $-N(CH_3)_2$, $-CH_2OH$, $-CH_2OCH_3$, or $-SO_n(C_1-C_4 \text{ alkyl})$, wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1-C_4 \text{ alkyl})$, $-CHO$, or $-COO(C_1-C_4 \text{ alkyl})$ wherein the C_1-C_4 alkyl moieties in the foregoing R_4 groups may optionally contain one carbon-carbon double or triple bond;
- 20

- R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, pyrimidyl, benzofuranyl, pyrazinyl or benzothiazolyl, wherein each one of said groups R_5 may optionally be substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl and C_1-C_6 alkoxy, or by one substituent selected from iodo, hydroxy, bromo, formyl, cyano, nitro, amino, trifluoromethyl, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_6)(C_1-C_2 \text{ alkyl})$, $-COO(C_1-C_4 \text{ alkyl})$, $-CO(C_1-C_4 \text{ alkyl})$, $-COOH$, $-SO_2NH(C_1-C_4 \text{ alkyl})$, $-SO_2N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$, $-SO_2NH_2$, $-NHSO_2(C_1-C_4 \text{ alkyl})$, $-S(C_1-C_6 \text{ alkyl})$ and $-SO_2(C_1-C_6 \text{ alkyl})$, wherein each of said C_1-C_4 alkyl and C_1-C_6 alkyl moieties in the foregoing R_5 groups may optionally be substituted with one to three fluorine atoms;
- 25
- 30

R_6 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, $-CH_2OH$, $-CH_2OCH_3$, or C_1-C_4 alkoxy;

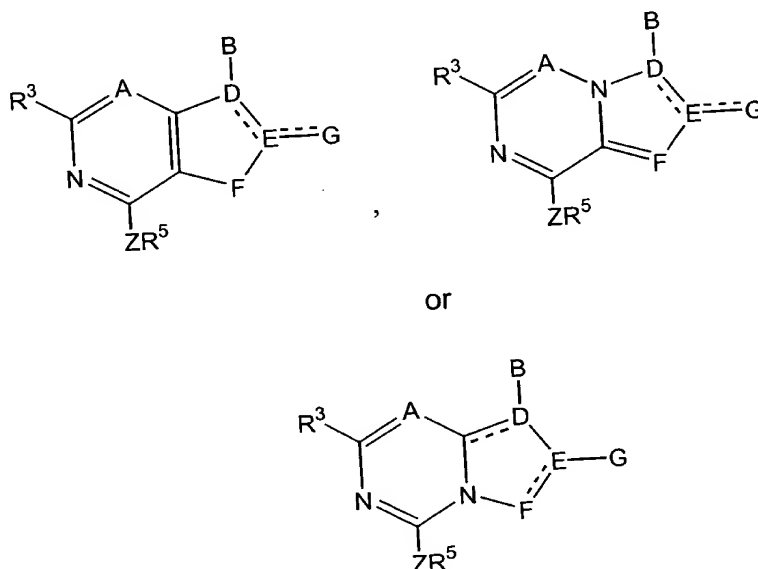
R_7 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, $-O(C_1$ - C_4 alkyl), cyano, $-CH_2OH$, $-CH_2O(C_1$ - C_2 alkyl), $-CO(C_1$ - C_2 alkyl), or $-COO(C_1$ - C_2 alkyl);

R_{11} is hydrogen, hydroxy, fluoro, or methoxy; and

R_{12} is hydrogen or C_1 - C_4 alkyl;

- 5 with the proviso that when A is N, then: (a) B is not unsubstituted alkyl; (b) R_5 is not unsubstituted phenyl or monosubstituted phenyl; and (c) R_3 is not unsubstituted alkyl.

- 10 Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



- 15 or a pharmaceutically acceptable salt thereof, wherein the dashed lines represent optional double bonds;
- A is nitrogen or CR^7 ;
- B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;
- 20 D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is either double bonded to E in formulas I and II or double bonded to the adjacent carbon atom common to both fused rings in formula III, or D is CH and is single bonded to E in formulas I and II;
- E is nitrogen, CH or carbon;

F is oxygen, sulfur, CHR^4 or NR^4 when it is single bonded to E and F is nitrogen or CR^4 when it is double bonded to E;

G, when single bonded to E, is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $-\text{S}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, NH_2 , $-\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$ or $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})(\text{C}_1\text{-C}_4 \text{ alkyl})$, wherein each of the $\text{C}_1\text{-C}_4$ alkyl groups of G may optionally be substituted with one hydroxy, $-\text{O}(\text{C}_1\text{-C}_2 \text{ alkyl})$ or fluoro group; G, when double bonded to E, is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D or F, is absent;

R^1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, $\text{C}_1\text{-C}_4$ alkoxy, CF_3 , $-\text{C}(=\text{O})\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{OC}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{OC}(=\text{O})\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{COOH}$, $-\text{COO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CON}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{S}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$ and $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, wherein each of the $\text{C}_1\text{-C}_4$ alkyl groups in the foregoing R^1 groups may optionally contain one or two double or triple bonds;

R^2 is $\text{C}_1\text{-C}_{12}$ alkyl which may optionally contain from one to three double or triple bonds, aryl or $(\text{C}_1\text{-C}_4 \text{ alkylene})\text{aryl}$, wherein said aryl and the aryl moiety of said $(\text{C}_1\text{-C}_4 \text{ alkylene})\text{aryl}$ is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; $\text{C}_3\text{-C}_8$ cycloalkyl or $(\text{C}_1\text{-C}_6 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$, wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said $(\text{C}_1\text{-C}_6 \text{ alkylene})(\text{C}_3\text{-C}_8 \text{ cycloalkyl})$ may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, $\text{C}_1\text{-C}_4$ alkyl, benzyl and $\text{C}_1\text{-C}_4$ alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and $\text{C}_1\text{-C}_4$ alkyl, or with one substituent selected from bromo, iodo, $\text{C}_1\text{-C}_6$ alkoxy, $-\text{OC}(=\text{O})(\text{C}_1\text{-C}_6 \text{ alkyl})$, $-\text{OC}(=\text{O})\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{S}(\text{C}_1\text{-C}_6 \text{ alkyl})$, amino, $-\text{NH}(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})\text{CO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{COOH}$, $-\text{COO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CONH}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{CON}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$, $-\text{SH}$, $-\text{CN}$, $-\text{NO}_2$, $-\text{SO}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4 \text{ alkyl})$ and $-\text{SO}_2\text{N}(\text{C}_1\text{-C}_4 \text{ alkyl})(\text{C}_1\text{-C}_2 \text{ alkyl})$;

$-\text{NR}^1\text{R}^2$ or $\text{CR}^1\text{R}^2\text{R}^{10}$ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two

of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1 - C_4 alkyl, benzyl or C_1 - C_4 alkanoyl;

R^3 is hydrogen, C_1 - C_4 alkyl, $-O(C_1$ - C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1 - C_4 alkyl) or $-SO_2(C_1$ - C_4 alkyl) wherein each of the (C_1 - C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1 - C_2 alkoxy);

each R^4 is, independently, hydrogen, (C_1 - C_6 alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, nitro, $-O(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), -S(C_1 - C_4 alkyl), $-SO(C_1$ - C_4 alkyl), $-SO_2(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), $-C(=O)H$ or $-C(=O)O(C_1$ - C_4 alkyl), wherein each of the (C_1 - C_6 alkyl) and (C_1 - C_4 alkyl) moieties in the foregoing R^4 groups may optionally contain one or two double or triple bonds and may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1 - C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH₃, fluoro, chloro, C_1 - C_3 thioalkyl, -CN, -COOH, $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl) and $-NO_2$;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3 - C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein Z^4 is hydrogen, C_1 - C_4 alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents R^{12} wherein one to three of said substituents may be selected, independently, from chloro, C_1 - C_6 alkyl and $-O(C_1$ - C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, $-CF_3$, $-NO_2$, $-NH_2$, $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_2 alkyl)(C_1 - C_6 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), -COOH, $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_2 alkyl)(C_1 - C_4 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein each of the C_1 - C_4 alkyl and C_1 - C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1 - C_4 alkyl, halo, cyano, hydroxy, $-O(C_1$ - C_4 alkyl) $-C(=O)(C_1$ - C_4 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$, $-CH_2O(C_1$ - C_4 alkyl);

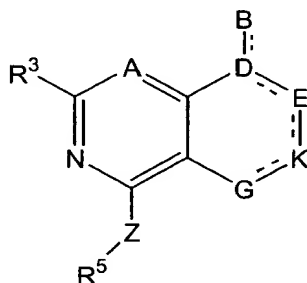
R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1 - C_4 alkyl; and

Z is NH, oxygen, sulfur, $-N(C_1-C_4 \text{ alkyl})$, $-NC(=O)(C_1-C_2 \text{ alkyl})$, $NC(=O)O(C_1-C_2 \text{ alkyl})$ or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

- 5 with the proviso that: (a) in the five membered rings of structures I, II and III, there can not be two double bonds adjacent to each other; and (b) when R^4 is attached to nitrogen, it is not halo, cyano or nitro.

- 10 Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



wherein the dashed lines represent optional double bonds;

or a pharmaceutically acceptable salt thereof, wherein

- 15 A is nitrogen or CR^7 ;
 B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$, and is single bonded to D; or B is $-CR^1R^2$, and is double bonded to D and D is carbon;
 D is nitrogen or CR^4 and is single bonded to all atoms to which it is attached,
 20 or D is carbon and is double bonded to E or double bonded to B;
 E is oxygen, nitrogen, sulfur, $C=O$, $C=S$, CR^6R^{12} , NR^6 or CR^6 ; or E is a two atom spacer, wherein one of the atoms is oxygen, nitrogen, sulfur, $C=O$, $C=S$, CR^6R^{12} , NR^6 or CR^6 , and the other is CR^6R^{12} or CR^9 ;
 K and G are each, independently, $C=O$, $C=S$, sulfur, oxygen, CHR^8 or NR^8
 25 when single bonded to both adjacent ring atoms, or nitrogen or CR^8 when it is double bonded to an adjacent ring atom;
 the 6- or 7-membered ring that contains D, E, K and G may contain from one to three double bonds, from zero to two heteroatoms selected from oxygen, nitrogen and sulfur, and from zero to two $C=O$ or $C=S$ groups, wherein the carbon atoms of

such groups are part of the ring and the oxygen and sulfur atoms are substituents on the ring;

R^1 is C_1 - C_6 alkyl optionally substituted with from one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, CF_3 ,
5 $-C(=O)(C_1-C_4\text{ alkyl})$, $-C(=O)-O-(C_1-C_4\text{ alkyl})$, $-OC(=O)(C_1-C_4\text{ alkyl})$, $-OC(=O)N(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$, $-NHCO(C_1-C_4\text{ alkyl})$, $-COOH$, $-COO(C_1-C_4\text{ alkyl})$, $-CONH(C_1-C_4\text{ alkyl})$, $-CON(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$, $-S(C_1-C_4\text{ alkyl})$, $-CN$, $-NO_2$, $-SO(C_1-C_4\text{ alkyl})$, $-SO_2(C_1-C_4\text{ alkyl})$, $-SO_2NH(C_1-C_4\text{ alkyl})$ and $-SO_2N(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$, wherein each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups may optionally contain one
10 or two double or triple bonds;

R^2 is C_1 - C_{12} alkyl which may optionally contain from one to three double or triple bonds, aryl or $(C_1-C_4\text{ alkylene})\text{aryl}$, wherein said aryl and the aryl moiety of said $(C_1-C_4\text{ alkylene})\text{aryl}$ is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl,
15 isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C_3 - C_8 cycloalkyl or $(C_1-C_6\text{ alkylene})(C_3-C_8\text{ cycloalkyl})$, wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said $(C_1-C_6\text{ alkylene})(C_3-C_8\text{ cycloalkyl})$ may optionally and independently be replaced by an oxygen or sulfur and wherein each of the foregoing R^2 groups may optionally be
20 substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1 - C_4 alkyl, or with one substituent selected from C_1 - C_6 alkoxy, $-OC(=O)(C_1-C_6\text{ alkyl})$, $-OC(=O)N(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$, $-S(C_1-C_6\text{ alkyl})$, amino, $-NH(C_1-C_2\text{ alkyl})$, $-N(C_1-C_2\text{ alkyl})(C_1-C_4\text{ alkyl})$, $-N(C_1-C_4\text{ alkyl})-CO-(C_1-C_4\text{ alkyl})$, $-NHCO(C_1-C_4\text{ alkyl})$, $-COOH$, $-COO(C_1-C_4\text{ alkyl})$, $-CONH(C_1-C_4\text{ alkyl})$, $-CON(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$, $-SH$, $-CN$, $-NO_2$, $-SO(C_1-C_4\text{ alkyl})$, $-SO_2(C_1-C_4\text{ alkyl})$, $-SO_2NH(C_1-C_4\text{ alkyl})$ and $-SO_2N(C_1-C_4\text{ alkyl})(C_1-C_2\text{ alkyl})$;
25

$-NR^1R^2$ or $CR^1R^2R^{10}$ may form a ring selected from saturated 3 to 8 membered rings, the 5 to 8 membered rings of which may optionally contain one or two double bonds, and wherein one or two of the ring carbon atoms of such 5 to 8
30 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen or C_1 - C_4 alkyl;

R^3 is hydrogen, C_1 - C_4 alkyl, $-O(C_1-C_4\text{ alkyl})$, chloro, fluoro, bromo, iodo, $-S(C_1-C_4\text{ alkyl})$ or $-SO_2(C_1-C_4\text{ alkyl})$;

R^4 is hydrogen, C_1 - C_2 alkyl, hydroxy or fluoro;

each R^6 , R^8 and R^9 that is attached to a carbon atom is selected, independently, from hydrogen, C_1 - C_2 alkyl, fluoro, chloro, bromo, iodo, hydroxy, hydroxymethyl, formyl, trifluoromethyl, cyano, amino, nitro, $-O(C_1$ - C_2 alkyl), $-N(C_1$ - C_2 alkyl)(C_1 - C_2 alkyl), $-S(C_1$ - C_2 alkyl), $-CO(C_1$ - C_2 alkyl), $-C(=O)H$ or $-C(=O)O(C_1$ - C_2 alkyl),
 5 wherein each of the C_1 - C_2 alkyl moieties in the foregoing R^6 , R^8 , and R^9 groups may optionally contain one double or triple bond; and each R^6 , R^8 , and R^9 that is attached to a nitrogen atom is selected, independently, from hydrogen and C_1 - C_4 alkyl;

R^5 is substituted phenyl, naphthyl, pyridyl or pyrimidyl, wherein each of the foregoing R^5 groups is substituted with from two to four substituents R^{15} , wherein
 10 from one to three of said substituents may be selected, independently, from chloro, C_1 - C_6 alkyl, $-O(C_1$ - C_6 alkyl) and $-(C_1$ - C_6 alkylene) $O(C_1$ - C_6 alkyl), and wherein one of said substituents may be selected, independently, from bromo, iodo, formyl, cyano, trifluoromethyl, nitro, amino, $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_2 alkyl)(C_1 - C_6 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), $-COOH$, $-SO_2NH(C_1$ - C_4 alkyl),
 15 $-SO_2N(C_1$ - C_2 alkyl)(C_1 - C_4 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein each of the C_1 - C_4 alkyl and C_1 - C_6 alkyl moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

20 R^7 is hydrogen, methyl, halo, hydroxy, methoxy, $-C(=O)(C_1$ - C_2 alkyl), $-C(=O)O(C_1$ - C_2 alkyl), trifluoromethoxy, hydroxymethyl, trifluoromethyl or formyl;

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

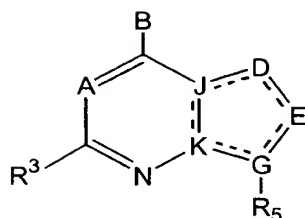
R^{11} is hydrogen or C_1 - C_4 alkyl;

R^{12} is hydrogen or methyl; and

25 Z is NH , oxygen, sulfur, $-N(C_1$ - C_4 alkyl), or $CR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, and methyl with the exception that one of R^{13} and R^{14} may optionally be cyano;

with the proviso that: (a) in the six or seven membered rings of structures in formula I, there can not be two double bonds adjacent to each other; and (b) when D
 30 is carbon and is double bonded to B , then B is CR^1R^2 .

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR⁷;

- 5 B is -NR¹R², -CR¹R²R¹⁰, -C(=CR²R¹¹)R¹, -NHCR¹R²R¹⁰, -OCR¹R²R¹⁰, -SCR¹R²R¹⁰, -CR²R¹⁰NHR¹, -CR²R¹⁰OR¹, -CR²R¹⁰SR¹ or -COR²;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens;

- 10 D and E are each selected, independently, from nitrogen, CR⁴, C=O, C=S, sulfur, oxygen, CR⁴R⁶ and NR⁸;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may

- 15 optionally have one or two C=O or C=S groups;

R¹ is C₁-C₆ alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C₁-C₄ alkyl), CF₃, -C(=O)O-(C₁-C₄alkyl), -OC(=O)(C₁-C₄ alkyl), -OC(=O)N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NHCO(C₁-C₄ alkyl), -COOH, -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₄ alkyl), -CN, -NO₂, -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl) and -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), wherein each of the C₁-C₄ alkyl groups in the foregoing R¹ groups may optionally contain one or two double or triple bonds;

- 25 R² is C₁-C₁₂ alkyl which may optionally contain from one to three double or triple bonds, aryl or (C₁-C₄ alkylene)aryl, wherein said aryl and the aryl moiety of said (C₁-C₄ alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C₃-C₈ cycloalkyl or (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), wherein one or two of the
30 carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said

- (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ² wherein Z² is selected from hydrogen, C₁-C₄ alkyl, benzyl and C₁-C₄ alkanoyl, and wherein each of the foregoing R² groups may optionally be substituted with from one to three substituents independently selected
- 5 from chloro, fluoro, hydroxy and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -OC(=O)(C₁-C₆ alkyl), -OC(=O)N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), amino, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)-CO-(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COOH, -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SH, -CN, -NO₂, -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl) and -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl);
- 10 -NR¹R² or CR¹R²R¹⁰ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ³ wherein Z³ is
- 15 hydrogen, C₁-C₄ alkyl, benzyl or C₁-C₄ alkanoyl;
- R³ is hydrogen, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), chloro, fluoro, bromo, iodo, (C₁-C₂ alkylene)-O-(C₁-C₂ alkyl), (C₁-C₂ alkylene)-OH, or -S(C₁-C₄ alkyl);
- each R⁴ is, independently, hydrogen, (C₁-C₆ alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C₁-C₂ alkylene)-OH, CF₃, CH₂SCH₃, nitro, -O(C₁-C₄ alkyl),
- 20 -N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -C(=O)H or -C(=O)O(C₁-C₄alkyl);
- R⁶ is hydrogen, methyl or ethyl;
- R⁸ is hydrogen or C₁-C₄ alkyl;
- R⁵ is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the
- 25 foregoing R⁵ groups is substituted with from one to four substituents R¹³ wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C₁-C₆ alkyl and -O(C₁-C₆ alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C₁-C₄ alkylene)-OH, (C₁-C₄alkylene)-O-(C₁-C₂ alkyl), -CN, -CF₃, -NO₂, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₆ alkyl), -OCO(C₁-C₄ alkyl),
- 30 (C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -S(C₁-C₆ alkyl), (C₁-C₄ alkylene)-S-(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -COOH, -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -SO₂NH₂, -NH₂SO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein each of the C₁-C₄ alkyl and C₁-C₆ alkyl moieties in the foregoing R⁵ groups may optionally have one or two double bonds;

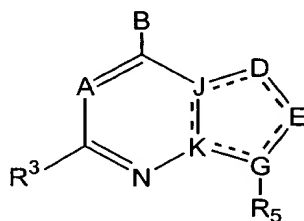
R^7 is hydrogen, C_1 - C_4 alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, $-O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$ or $-CH_2O(C_1$ - C_2 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

5 R^{11} is hydrogen or C_1 - C_4 alkyl; and

with the proviso that: a) when both J and K are carbons and D is CR^4 and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR^4 or $C=O$ or $C=S$; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a
15 compound of formula:



or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is nitrogen or CR^7 ;

20 B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $-CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

J and K are each independently nitrogen or carbon and both J and K are not nitrogens;

D and E are each selected, independently, from nitrogen, CR^4 , $C=O$, $C=S$,
25 sulfur, oxygen, CR^4R^6 and NR^8 ;

G is nitrogen or carbon;

the ring containing D, E, G, K, and J in formula I may be a saturated or unsaturated 5-membered ring and may optionally contain one or two double bonds and may optionally contain from one to three heteroatoms in the ring and may
30 optionally have one or two $C=O$ or $C=S$ groups;

R¹ is C₁-C₆ alkyl optionally substituted with one or two substituents independently selected from hydroxy, fluoro, chloro, bromo, iodo, -O-(C₁-C₄ alkyl), CF₃, -C(=O)O-(C₁-C₄alkyl), -OC(=O)(C₁-C₄ alkyl), -OC(=O)N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NHCO(C₁-C₄ alkyl), -COOH, -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₄ alkyl), -CN, -NO₂, -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl) and -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), wherein each of the C₁-C₄ alkyl groups in the foregoing R¹ groups may optionally contain one or two double or triple bonds;

R² is C₁-C₁₂ alkyl which may optionally contain from one to three double or triple bonds, aryl or (C₁-C₄ alkylene)aryl, wherein said aryl and the aryl moiety of said (C₁-C₄ alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; C₃-C₈ cycloalkyl or (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ² wherein Z² is selected from hydrogen, C₁-C₄ alkyl, benzyl and C₁-C₄ alkanoyl, and wherein each of the foregoing R² groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -OC(=O)(C₁-C₆ alkyl), -OC(=O)N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), amino, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)-CO-(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COOH, -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SH, -CN, -NO₂, -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl) and -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl);

-NR¹R² or CR¹R²R¹⁰ may form a saturated 3 to 8 membered carbocyclic ring which may optionally contain from one to three double bonds and wherein one or two of the ring carbon atoms of such 5 to 8 membered rings may optionally and independently be replaced by an oxygen or sulfur atom or by NZ³ wherein Z³ is hydrogen, C₁-C₄ alkyl, benzyl or C₁-C₄ alkanoyl;

R³ is hydrogen, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), chloro, fluoro, bromo, iodo, (C₁-C₂ alkylene)-O-(C₁-C₂ alkyl), (C₁-C₂ alkylene)-OH, or -S(C₁-C₄ alkyl);

each R⁴ is, independently, hydrogen, (C₁-C₆ alkyl), fluoro, chloro, bromo, iodo, hydroxy, cyano, amino, (C₁-C₂ alkylene)-OH, CF₃, CH₂SCH₃, nitro, -O(C₁-C₄ alkyl),

-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -C(=O)H or -C(=O)O(C₁-C₄alkyl);

R⁶ is hydrogen, methyl or ethyl;

R⁸ is hydrogen or C₁-C₄ alkyl;

- 5 R⁵ is phenyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and wherein each of the foregoing R⁵ groups is substituted with from one to four substituents R¹³ wherein one to three of said substituents may be selected, independently, from fluoro, chloro, C₁-C₆ alkyl and -O(C₁-C₆ alkyl) and one of said substituents may be selected from bromo, iodo, formyl, OH, (C₁-C₄ alkylene)-OH, (C₁-C₄alkylene)-O-(C₁-C₂ alkyl), -CN, 10 -CF₃, -NO₂, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₆ alkyl), -OCO(C₁-C₄ alkyl), (C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -S(C₁-C₆ alkyl), (C₁-C₄ alkylene)-S-(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -COOH, -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and -SO₂(C₁-C₆ alkyl), and wherein each of the C₁-C₄ alkyl and C₁-C₆ alkyl moieties in the 15 foregoing R⁵ groups may optionally have one or two double bonds;

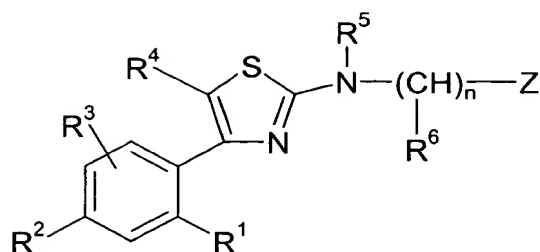
R⁷ is hydrogen, C₁-C₄ alkyl, halo (e.g., chloro, fluoro, iodo or bromo), hydroxy, -O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -C(=O)O(C₁-C₄ alkyl), -OCF₃, -CF₃, -CH₂OH or -CH₂O(C₁-C₂ alkyl);

R¹⁰ is hydrogen, hydroxy, methoxy or fluoro;

- 20 R¹¹ is hydrogen or C₁-C₄ alkyl; and

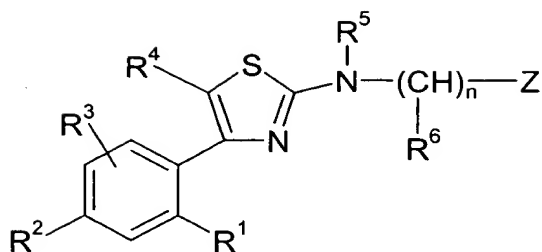
with the proviso that: a) when both J and K are carbons and D is CR⁴ and E is nitrogen, then G can not be nitrogen; (b) when both J and K are carbons and D and G are nitrogens, then E can not be CR⁴ or C=O or C=S; (c) when both J and K are carbons and D and E are carbons, then G can not be nitrogen; (d) when G is carbon, 25 it must be double banded to E; and (e) in the ring containing J, K, D, E and G, there can not be two double bonds adjacent to each other.

- Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a 30 compound of formula:



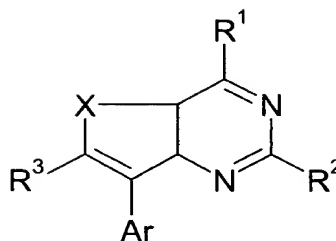
wherein each of R^1 and R^2 is independently a halogen atom; a C_1 - C_5 hydroxyalkyl radical; C_1 - C_5 alkyl; C_7 - C_{10} aralkyl; C_1 - C_5 alkoxy; trifluoromethyl; nitro; nitrile; a group -SR where R is hydrogen, a C_1 - C_5 alkyl radical or a C_7 - C_{10} aralkyl radical; a group S-CO-R where R is a C_1 - C_5 alkyl radical or aralkyl in which the aryl portion is C_6 - C_8 and the alkyl portion is C_1 - C_4 ; a group -COOR' where R' is hydrogen or C_1 - C_5 alkyl; a group -CONR'R'' where R' and R'' are as defined above for R'; a group -NR'R'' where R' and R'' are as previously defined for R'; a group -CONRaRb or NRaRb, where Ra and Rb, taken together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring; or a group -NHCO-NR'R'', where R' and R'' are as defined above for R'; R^3 is hydrogen or as defined for R^1 and R^2 is a hydrogen atom; C_{1-5} alkyl; halogen; a hydroxymethyl group; or a formyl group; R^5 is C_1 - C_5 alkyl; a C_3 - C_7 cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl portion is C_3 - C_7 and the alkyl portion is C_1 - C_5 ; or C_5 - C_6 alkenyl; n is 0 or 1; R^6 is C_{1-5} alkyl; alkoxyalkyl in which the alkyl portions are C_1 - C_5 ; C_3 - C_7 cycloalkyl; a cycloalkylalkyl group in which the cycloalkyl portion is C_3 - C_7 and the alkyl portion is C_1 - C_5 ; a cycloalkyloxyalkyl radical in which the cycloalkyl is C_3 - C_7 and the alkyl is C_1 - C_4 ; a hydroxyalkyloxyalkyl radical in which the alkyls are C_2 - C_{10} ; or an alkoxyalkyloxyalkyl radical in which the alkyls are C_3 - C_{12} ; and Z is an optionally substituted bi- or tricyclic aromatic or heteroaromatic group; or a stereoisomer or addition salt thereof.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



- wherein each of R^1 and R^2 is independently a halogen atom; a C_1 - C_5 hydroxyalkyl radical; C_1 - C_5 alkyl; C_7 - C_{10} aralkyl; C_1 - C_5 alkoxy; trifluoromethyl; nitro; nitrile; a group -SR where R is hydrogen, a C_1 - C_5 alkyl radical or a C_7 - C_{10} aralkyl radical; a group S-CO-R where R is a C_1 - C_5 alkyl radical or aralkyl in which the aryl portion is C_6 - C_8 and the alkyl portion is C_1 - C_4 ; a group -COOR' where R' is hydrogen or C_1 - C_5 alkyl; a group -CONR'R'' where R' and R'' are as defined above for R'; a group -NR'R'' where R' and R'' are as previously defined for R'; a group -CONRaRb or NRaRb, where Ra and Rb, taken together with the nitrogen atom to which they are attached, form a 5- to 7-membered heterocyclic ring; or a group -NHCO-NR'R'', where R' and R'' are as defined above for R'; R^3 is hydrogen or as defined for R^1 and R^2 is a hydrogen atom; C_{1-5} alkyl; halogen; a hydroxymethyl group; or a formyl group; R^5 is C_1 - C_5 alkyl; a C_3 - C_7 cycloalkyl group; a cycloalkylalkyl group in which the cycloalkyl portion is C_3 - C_7 and the alkyl portion is C_1 - C_5 ; or C_5 - C_6 alkenyl; n is 0 or 1; R^6 is C_{1-5} alkyl; alkoxyalkyl in which the alkyl portions are C_1 - C_5 ; C_3 - C_7 cycloalkyl; a cycloalkylalkyl group in which the cycloalkyl portion is C_3 - C_7 and the alkyl portion is C_1 - C_5 ; a cycloalkyloxyalkyl radical in which the cycloalkyl is C_3 - C_7 and the alkyl is C_1 - C_4 ; a hydroxyalkyloxyalkyl radical in which the alkyls are C_2 - C_{10} ; or an alkoxyalkyloxyalkyl radical in which the alkyls are C_3 - C_{12} ; and Z is an optionally substituted bi- or tricyclic aromatic or heteroaromatic group; or a stereoisomer or addition salt thereof.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of formula:



or a stereoisomer or pharmaceutically acceptable acid addition salt form thereof, wherein

- 5 X is S, SO or SO₂;
 R¹ is NR⁴R⁵ or OR⁵;
 R² is C₁-C₆alkyl, C₁-C₆alkyloxy or C₁-C₆alkylthio;
 R³ is hydrogen, C₁-C₆alkyl, C₁-C₆alkylsulfonyl, C₁-C₆alkylsulfoxy or C₁-C₆alkylthio;
 R⁴ is hydrogen, C₁₋₆alkyl, mono- or di(C₃-C₆cycloalkyl)methyl, C₃-C₆cycloalkyl, C₃-C₆alkenyl, hydroxyC₁-C₆alkyl, C₁-C₆alkylcarbonyloxyC₁-C₆alkyl or C₁-C₆alkyloxyC₁-C₆alkyl;
 10 R⁵ is C₁-C₈alkyl, mono- or di(C₃-C₆cycloalkyl)methyl, Ar¹CH₂, C₃-C₆alkenyl, C₁-C₆alkyloxyC₁-C₆alkyl, hydroxyC₁-C₆alkyl, thienylmethyl, furanylmethyl, C₁-C₆alkylthioC₁-C₆alkyl, morpholinyl, mono- or di(C₁-C₆alkyl)aminoC₁-C₆alkyl, di(C₁-C₆alkyl)amino, C₁-C₆alkylcarbonylC₁-C₆alkyl, C₁-C₆alkyl substituted with imidazolyl; or
 15 a radical of formula -Alk-O-CO-Ar I;
 or R⁴ and R⁵ taken together with the nitrogen atom to which they are attached may form a pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl group, optionally substituted with C₁-C₆alkyl or C₁-C₆alkyloxyC₁-C₆alkyl;
 20 Ar is phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁-C₆alkyl, trifluoromethyl, hydroxy, cyano, C₁-C₆alkyloxy, benzyloxy, C₁-C₆alkylthio, nitro, amino and mono- or di(C₁-C₆alkyl)amino; pyridinyl; pyridinyl substituted with 1, 2 or 3 substituents independently selected from halo, C₁-C₆alkyl, trifluoromethyl, hydroxy, cyano, C₁-C₆alkyloxy, benzyloxy, C₁-C₆alkylthio, nitro, amino, mono- or di(C₁-C₆alkyl)amino and piperidinyl; and wherein said
 25 substituted phenyl may optionally be further substituted with one or more halogens;
 Ar¹ is phenyl; phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, C₁-C₆alkyl, C₁-C₆alkyloxy, di(C₁-C₆alkyl)aminoC₁-C₆alkyl trifluoromethyl, and C₁-C₆alkyl substituted with morpholinyl; or pyridinyl; and

Alk is C₁-C₆alkanediyl.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound selected from the group consisting of:

- 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
- butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
- 4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;
- 4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
- N-butyl-N-ethyl-2,5-dimethyl-NN-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
- [4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
- 6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one;
- 3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;
- diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- 2-[butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;
- dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

- butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
- 4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;
- n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- 2-[N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino]-ethanol;
- 4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
- n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
- 2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-ethyl-propyl)amine;
- butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
- [3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
- 4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
- (1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;

- 4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
- 4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
- 5 4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine;
- 2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
- 1- (1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-
- 10 imidazo[4,5-c]pyridin-2-one;
- 9-(1-ethylpropyl)-2-methyl-6-(2,4,6-trimethylphenylamino)-7,9-dihydro-purin-8-one;
- 1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 15 1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1H-imidazo[4,5-c]pyridine;
- 1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-(1-ethylpropyl)-3,6-dimethyl-4-(2,4,6-trimethylphenylamino)-1,3-dihydro-
- 20 imidazo[4,5-c]pyridin-2-one;
- 1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-pyrido[3,4-b]pyrazin-3-one;
- 1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
- 25 1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
- 1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid methyl ester;
- 1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetra-
- 30 hydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
- 1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-[1,6]naphthyridin-2-one;
- 1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine;

1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;

5 1-(1-ethyl-propyl)-3,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-3,4-dihydro-1H-3-oxa-[1,6]-naphthyridin-2-one;

1-(1-ethyl-propyl)-3,3,6-trimethyl-4-(2,4,6-trimethyl-phenoxy)-2,3-dihydro-1H-pyrrolo[3,2-c]pyridine;

10 7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;

15 7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-ethyl-propyl-amine;

20 [6-bromo-5-bromomethyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-amine;

[6-bromo-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-methyl-amine;

25 7-(1-ethyl-propoxy)-5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-[1,2,3]triazolo[4,5-b]pyridine;

4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

30 (\pm)-2,5-dimethyl-4-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-dimethyl-4-(S)-(tetrahydro-furan-3-yloxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo-[3,2-d]pyrimidine;

2,5-dimethyl-4-(1-propyl-butoxy)-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;

- 4-sec-butylsulfanyl-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
- 4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
- 5 8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b] pyrazin-2-one;
- 8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;
- 4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
- 10 5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
- 5-(1-ethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
- 8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-
- 15 tetrahydro-pyrido[2,3-b]pyrazine;
- (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
- 4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
- 4-(butyl-ethyl-amino)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6
- 20 H- pyrido[2,3-d]pyrimidin-7-one;
- 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
- (butyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
- 25 (propyl-ethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d]pyrimidin-4-yl]-amine;
- (diethyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro-pyrido [2,3-d]pyrimidin-4-yl]-amine;
- (1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-
- 30 tetrahydro- pyrido[2,3-d]pyrimidin-4-yl]-amine;
- (1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-5,6,7,8-tetrahydro- pyrido[2,3-d]pyrimidine;
- 4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;

- 4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido [2,3-d]pyrimidin-7-one;
- (butyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
- 5 (propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-[2,3-d] pyrimidin-4-yl]-amine;
- (diethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
- 10 (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidin-4-yl]-amine;
- (1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;
- 8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;
- 15 8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro- pyrido[2,3-b]pyrazine;
- 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinoline;
- 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;
- 20 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-bromo-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;
- 8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-bromo-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;
- (1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-bromo-phenyl)-quinolin-4-yl]-
- 25 amine;
- 4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,6-dimethyl-4-chloro-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
- 8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;
- 30 8-(1-ethyl-propoxy)-6-methyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro- pyrido[2,3-b]pyrazine;
- 4-(1-ethyl-propoxy)-2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinoline;
- 5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5-(1-ethyl-propoxy)-7-methyl-1-(2,6-dimethyl-4-chloro-phenyl)-1,2-dihydro-3-oxa-1,8-diaza-naphthalen-4-one;

8-(1-ethyl-propoxy)-1,6-dimethyl-4-(2,6-dimethyl-4-chloro-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

5 (1-ethyl-propyl)-[2-methyl-8-(2,6-dimethyl-4-chloro-phenyl)-quinolin-4-yl]-amine;

8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

10 8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

15 8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido [2,3-b]pyrazin-2-one;

20 8-(1-hydroxymethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(1-ethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

25 8-diethylamino-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

8-(ethyl-propyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

30 8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido[2,3-b]pyrazine;

4-(1-hydroxymethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

4-(1-ethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

- 4-diethylamino-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(ethyl-propyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
4-(butyl-ethyl-amino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
5-(1-hydroxymethyl-propoxy)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-
5 2H-3-oxa-1,8-diaza-naphthalene;
5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-
dihydro-2H-3-oxa-1,8-diaza-naphthalene;
5-(1-ethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-
oxa-1,8-diaza-naphthalene;
10 5-diethylamino-5-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-
diaza-naphthalene;
5-(ethyl-propyl-amino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-
oxa-1,8-diaza-naphthalene;
8-(butyl-ethyl-amino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-
15 oxa-1,8-diaza-naphthalene;
4-(2,4-dichlorophenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)
methyl)-N-propylamino]thiazole;
oxalate of 4-(2,4-dichlorophenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-yl)-N-
propylamino]thiazole;
20 oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methylisoquinol-5-
yl)-N-propylamino]thiazole;
4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-methoxycarbonylmethylindol-
5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-
25 5-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-chloroisoquinol-5-
yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-methoxyisoquinol-5-
yl)-N-propylamino]thiazole;
30 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-
1-methoxynaphth-2-yl)-N-propylamino]thiazole;
oxalate of 4-(2-chloro-4-trifluoromethylphenyl)-5-methyl-2-[N-6-
methoxyisoquinol-5-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2-ethoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,3-dimethylnaphth-1-yl)-N-propylamino]thiazole;

5 chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(6-bromo-2-methoxynaphth-1-yl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(2,6-dimethylnaphth-1-yl)-N-propylamino]thiazole;

10 chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(methoxymethyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

chlorhydrate of 4-(2-chloro-4-methoxyphenyl)-5-methyl-2-[N-(1-(cyclopropyl)-1-(naphth-2-yl)methyl)-N-propylamino]thiazole;

3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

15 3-(2,4-dichlorophenyl)-5-methyl-7-(N-allyl-N-cyclopropanemethylamino)-pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N,N-diallylamino)-pyrazolo[2,3-a]pyrimidine;

20 2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-butyl-N-cyclopropane-methyl-amino)pyrazolo[2,3-a]pyrimidine;

2-methylthio-3-(2,4-dichlorophenyl)-5-methyl-7-(N-propyl-N-cyclopropane-methyl-amino)pyrazolo[2,3-a]pyrimidine;

2-methyl-3-(4-chlorophenyl)-5-methyl-7-(N,N-dipropylamino)-pyrazolo[2,3-a]pyrimidine;

25 3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidine-7-amine;

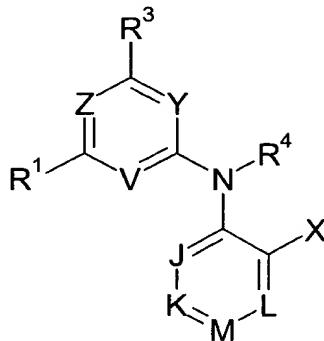
30 3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methoxyethylamino)-pyrazolo(2,3-a)pyrimidine;

7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine;

7-(N-(3-cyanopropyl)-N-propylamino-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine;

- [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-
amine;
- 5 cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-
a]pyrimidin-7-yl]-propyl-amine;
cyclopropylmethyl-[3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-
a]pyrimidin-7-yl]-propyl-amine;
cyclopropylmethyl-[3-(2,4-di-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-
a]pyrimidin-7-yl]-propyl-amine;
- 10 [3-(2-methyl-4-chloro-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-
di-propyl-amine;
[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-
propyl)-amine;
[2,5-dimethyl-3-(2,4-dichloro-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-
15 propyl)-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid
methyl ester;
3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-propyl-N-
cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine; and
- 20 3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N-ethyl-N-
cyclopropylmethyl-pyrazolo[2,3-a]pyrimidin-7-amine.

Another group of useful CRF antagonists for use in the compositions,
methods, and kits of the present invention are those wherein the CRF antagonist is a
25 compound of the following formula, disclosed in WO 95/10506:



or a pharmaceutically acceptable salt or prodrug thereof, wherein Y is CR^{3a}, N, or CR²⁹;

when Y is CR^{3a} or N:

R¹ is independently selected at each occurrence from the group consisting of
 5 C₁-C₄ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, halogen, C₁-C₂ haloalkyl, NR⁶R⁷, OR⁸, and S(O)_nR⁸;

R³ is C₁-C₄ alkyl, aryl, C₃-C₆ cycloalkyl, C₁-C₂ haloalkyl, halogen, nitro, NR⁶R⁷, OR⁸, S(O)_nR⁸ C(=O)R⁹, C(=O)NR⁶R⁷, C(=S)NR⁶R⁷, -(CHR¹⁶)_kNR⁶R⁷, (CH₂)_kOR⁸, C(=O)NR¹⁰CH(R¹¹)CO₂R¹², -C(OH)(R²⁵)(R^{25a}), -(CH₂)_pS(O)_n-alkyl, -(CHR¹⁶)R²⁵,
 10 -C(CN)(R²⁵)(R¹⁶) provided that R²⁵ is not -NH- containing rings, -C(=O)R²⁵, -CH(CO₂R¹⁶)₂, NR¹⁰C(=O)CH(R¹¹)NR¹⁰R¹², NR¹⁰CH(R¹¹)CO₂R¹²; substituted C₁-C₄ alkyl, substituted C₂-C₄ alkenyl, substituted C₂-C₄ alkynyl, substituted C₁-C₄ alkoxy, aryl-(substituted C₁-C₄) alkyl, aryl-(substituted C₁-C₄) alkoxy, substituted C₃-C₆ cycloalkyl, amino-(substituted C₁-C₄)alkyl, substituted C₁-C₄ alkylamino, where
 15 substitution by R²⁷ can occur on any carbon containing substituent; 2-pyridinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidiny, phenyl, 1*H*-indazolyl, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl, 3*H*-indolyl, 4-piperidonyl, 4*aH*-carbazolyl,
 20 4*H*-quinoliziny, 6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, furazanyl, imidazolidinyl, indoliny, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindoliny, isoindolyl, isoquinoliny, benzimidazolyl, isothiazolyl, isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxazolidinyl, oxazolyl,
 25 phenanthridiny, phenanthroliny, phenaziny, phenoxathiiny, phenoxazinyl, phthalazinyl, piperaziny, piperidiny, pteridiny, puriny, pyranly, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyrimidiny, pyrrolidinyl, pyrroliny, pyrroly, quinazoliny, quinoliny, quinoxaliny, quinuclidiny, β-carboliny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, thianthrenyl, thiazolyl,
 30 thiophenyl, triazinyl, xanthenyl; or 1-tetrahydroquinoliny or 2-tetrahydroisoquinoliny either of which can be substituted with 0-3 groups chosen from keto and C₁-C₄ alkyl;

J, K, and L are independently selected at each occurrence from the group of N, CH, and CX';

M is CR⁵ or N;

V is CR^{1a} or N;

Z is CR² or N;

R^{1a}, R², and R^{3a} are independently selected at each occurrence from the group consisting of hydrogen, halo, halomethyl, C₁-C₃ alkyl, and cyano;

5 R⁴ is (CH₂)_mOR¹⁶, C₁-C₄ alkyl, allyl, propargyl, (CH₂)_mR¹³, or -(CH₂)_mOC(O)R¹⁶;

X is halogen, aryl, heteroaryl, S(O)₂R⁸, SR⁸, halomethyl, -(CH₂)_pOR⁸, cyano, -(CHR¹⁶)_pNR¹⁴R¹⁵, -C(=O)R⁸, C₁-C₆ alkyl, C₄-C₁₀ cycloalkylalkyl, C₁-C₁₀alkenyl, C₂-C₁₀alkynyl, C₂-C₁₀alkoxy, aryl-(C₂-C₁₀)-alkyl, C₃-C₆cycloalkyl, aryl-(C₁-C₁₀)-alkoxy, nitro, thio-(C₁-C₁₀)-alkyl, -C(=NOR¹⁶)-C₁-C₄-alkyl, -C(=NOR¹⁶)H, or -C(=O)NR¹⁴R¹⁵,

10 where substitution by R¹⁸ can occur on any carbon containing substituents;

X' is independently selected at each occurrence from the group consisting of hydrogen, halogen, aryl, heteroaryl, S(O)_nR⁸, halomethyl, -(CHR¹⁶)_pOR⁸, cyano, -(CHR¹⁶)_pNR¹⁴R¹⁵, C(=O)R⁸, C₁-C₆ alkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, C₁-C₁₀alkoxy, aryl-(C₁-C₁₀)-alkyl, C₃-C₆cycloalkyl, aryl-(C₁-C₁₀)-alkoxy, nitro, thio-(C₁-C₁₀)-alkyl, -C(=NOR¹⁶)-C₁-C₄-alkyl, -C(=NOR¹⁶)H, and -C(=O)NR¹⁴R¹⁵, where substitution by R¹⁶ can occur on any carbon containing substituents;

15 R⁵ is halo, -C(=NOR¹⁶)-C₁-C₄-alkyl, C₁-C₄alkyl, C₁-C₃ haloalkyl, -(CHR¹⁶)_pOR⁸, -(CHR¹⁶)_pS(O)_nR⁸, -(CHR¹⁶)_pNR¹⁴R¹⁵, C₃-C₆ cycloalkyl, C₂-C₁₀alkenyl, C₂-C₁₀alkynyl, aryl-(C₂-C₁₀)-alkyl, aryl-(C₁-C₁₀)-alkoxy, cyano, C₃-C₆ cycloalkoxy, nitro, amino-(C₂-C₁₀)-alkyl, thio-(C₂-C₁₀)-alkyl, SO_n(R⁸), C(=O)R⁸ -C(=NOR¹⁶)H, or -C(=O)NR¹⁴R¹⁵, where substitution by R¹⁸ can occur on any carbon containing substituents;

20 R⁶ and R⁷ are independently selected at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, C₁-C₆ alkoxy, (C₄-C₁₂)-cycloalkylalkyl, -(CH₂)_kR¹³, (CHR¹⁶)_pOR⁸, -(C₁-C₆alkyl)-aryl, heteroaryl, -S(O)_z-aryl or -(C₁-C₆alkyl)-heteroaryl or aryl, wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from the group consisting of hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, NHC(=O)(C₁-C₆ alkyl), NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, nitro, carboxy, CO₂(C₁-C₆ alkyl), cyano, and S(O)₂-(C₁-C₆-alkyl); or can be taken together to form -(CH₂)_pA(CH₂)_r-, optionally
25 substituted with 0-3 R¹⁷; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted on carbon with 1-3 groups consisting of hydrogen, C₁-C₆ alkyl, hydroxy, or C₁-C₆ alkoxy;

30 A is CH₂, O, NR²⁵, C(=O), S(O)_n, N(C(=O)R¹⁷), N(R¹⁹), C(H)(NR¹⁴R¹⁵), C(H)(OR²⁰), C(H)(C(=O)R²¹), or N(S(O)_nR²¹);

R^8 is independently selected at each occurrence from the group consisting of hydrogen; C_1 - C_6 alkyl; $-(C_4-C_{12})$ cycloalkylalkyl; $(CH_2)_l R^{22}$; C_3 - C_{10} cycloalkyl; $-NR^6 R^7$; aryl; heteroaryl; $-NR^{16}(CH_2)_n R^6 R^7$; $-(CH_2)_k R^{25}$; and $(CH_2)_l$ heteroaryl or $(CH_2)_l$ aryl, either of which can optionally be substituted with 1-3 groups selected from the group
 5 consisting of hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, amino, $NHC(=O)(C_1-C_6$ alkyl), $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl) $_2$, nitro, carboxy, $CO_2(C_1-C_6$ alkyl), cyano, and $S(O)_2(C_1-C_6$ -alkyl);

R^9 is independently selected at each occurrence from R^{10} , hydroxy, C_1 - C_4 alkoxy, C_3 - C_6 cycloalkyl, C_2 - C_4 alkenyl, aryl substituted with 0-3 R^{18} , and $-(C_1-C_6$ alkyl)-aryl substituted with 0-3 R^{18} ;
 10

R^{10} , R^{16} , R^{23} , and R^{24} are independently selected at each occurrence from hydrogen or C_1 - C_4 alkyl;

R^{11} is C_1 - C_4 alkyl substituted with 0-3 groups chosen from the following: keto, amino, sulfhydryl, hydroxyl, guanidiny, p-hydroxyphenyl, imidazolyl, phenyl, indolyl, and indoliny, or, when taken together with an adjacent R^{10} , are $(CH_2)_i$;
 15

R^{12} is hydrogen or an appropriate amine protecting group for nitrogen or an appropriate carboxylic acid protecting group for carboxyl;

R^{13} is independently selected at each occurrence from the group consisting of CN, OR^{19} , SR^{19} , and C_3 - C_6 cycloalkyl;

R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C_4 - C_{10} , cycloalkyl-alkyl, and R_{19} ;
 20

R^{17} is independently selected at each occurrence from the group consisting of R^{10} , C_1 - C_4 alkoxy, halo, OR^{23} , SR^{23} , $NR^{23} R^{24}$, and (C_1-C_6) alkyl (C_1-C_4) alkoxy;

R^{18} is independently selected at each occurrence from the group consisting of R^{10} , hydroxy, halogen, C_1 - C_2 haloalkyl, C_1 - C_4 alkoxy, $C(=O)R^{24}$, and cyano;
 25

R^{19} is independently selected at each occurrence from the group consisting of C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $(CH_2)_w R^{22}$, and aryl substituted with 0-3 R^{18} ;

R^{20} is independently selected at each occurrence from the group consisting of R^{10} , $C(=O)R^{31}$, and C_2 - C_4 alkenyl;

R^{21} is independently selected at each occurrence from the group consisting of R^{10} , C_1 - C_4 alkoxy, $NR^{23} R^{24}$, and hydroxyl;
 30

R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24} , SR^{24} , $NR^{23} R^{24}$, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $-S(O)_n R^{31}$, and $-C(=O)R^{25}$;

R^{25} , which can be optionally substituted with 0-3 R^{17} , is independently selected at each occurrence from the group consisting of phenyl, pyrazolyl, imidazolyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl, 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-pheno-thiazinyl, 4-pyrazinyl, azetidiny, 1*H*-indazolyl, 2-pyrrolidonyl, 2*H*,6*H*-1,5,2-dithiazinyl, 2*H*-pyrrolyl, 3*H*-indolyl, 4-piperidonyl, 4*aH*-carbazolyl, 4*H*-quinolizinyl, 6*H*-1,2,5-thiadiazinyl, acridinyl, azocinyl, azepinyl, benzofuranyl, benzothiophenyl, carbazolyl, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, furazanyl, indoliny, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindoliny, isoindolyl, isoquinoliny, benzimidazolyl, isothiazolyl, isoxazolyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxazolidiny, oxazolyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, pteridiny, puriny, pyranly, pyrazolidiny, pyridaziny, pyridyl, pyrimidiny, pyrrolidiny, pyrroliny, pyrrolyl, quinazoliny, quinoliny, quinoxaliny, quinuclidiny, B-carboliny, tetrahydrofuranyl, tetrazolyl, thianthrenyl, thiazolyl, thiophenyl, triaziny, xanthenyl; and 1-tetrahydroquinoliny or 2-tetrahydroisoquinoliny either of which can be substituted with 0-3 groups chosen from keto and C_1 - C_4 alkyl;

R^{25a} , which can be optionally substituted with 0-3 R^{17} , is independently selected at each occurrence from the group consisting of H and R^{25} ;

R^{27} is independently selected at each occurrence from the group consisting of C_1 - C_3 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_2 - C_4 alkoxy, aryl, nitro, cyano, halogen, aryloxy, and heterocycle optionally linked through O;

R^{31} is independently selected at each occurrence from the group consisting of C_1 - C_4 alkyl, C_3 - C_7 cycloalkyl, C_4 - C_{10} cycloalkyl-alkyl, and aryl- (C_1-C_4) alkyl;

k, m, and r are independently selected at each occurrence from 1-4;
n is independently, selected at each occurrence from 0-2,
p, q, and z are independently selected at each occurrence from 0-3;
t and w are independently selected at each occurrence from 1-6,
provided that when J is CX' and K and L are both CH, and M is CR^5 , then

(A) when V and Y are N and Z is CH and R^1 and R^3 are methyl,
(1) and R^4 is methyl, then
(a) R^5 can not be methyl when X is OH and X' is H;
(b) R^5 can not be $-NHCH_3$, or $-N(CH_3)_2$ when X and X' are $-OCH_3$; and

- (c) R^5 can not be $-N(CH_3)_2$ when X and X' are $-OCH_2CH_3$;
 (2) and R^4 is ethyl, then
 (a) R^5 can not be methylamine when X and X' are $-OCH_3$;
 (b) R^5 can not be OH when X is Br and X' is OH; and
 5 (c) R^5 can not be $-CH_2OH$ or $-CH_2N(CH_3)_2$ when X is $-SCH_3$ and X' is H;
 (B) when V and Y are N, Z is CH, R^4 is ethyl, R^5 is iso-propyl, X is Br, X' is H, and
 (1) R^1 is CH_3 , then
 (a) R^3 can not be OH, piperazin-1-yl, $-CH_2$ -piperidin-1-yl,
 10 $-CH_2$ -(N-4-methylpiperazin-1-yl), $-C(O)NH$ -phenyl, $-CO_2H$,
 $-CH_2O$ -(4-pyridyl), $-C(O)NH_2$, 2-indolyl, $-CH_2O$ -(4-carboxyphenyl),
 $-N(CH_2CH_3)$ (2-bromo-4-isopropylphenyl);
 (2) R^2 is $-CH_2CH_2CH_3$ then R^3 can not be $-CH_2CH_2CH_3$
 (C) when V, Y and Z are N, R^4 is ethyl, and
 15 (1) R^5 is iso-propyl, X is bromo, and X' is H, then
 (a) R^3 can not be OH or $-OCH_2CN$ when R^1 is CH_3 and
 (b) R^3 can not be $-N(CH_3)_2$ when R^1 is $-N(CH_3)_2$;
 (2) R^5 is $-OCH_3$, X is $-OCH_3$, and X' is H, then R^3 and R^1 can not
 both be chloro;
 20 further provided that when J, K, and L are all CH and M is CR^5 , then
 (D) at least one of V, Y, and Z must be N;
 (E) when V is CR^{1a} , Z and Y can not both be N;
 (F) when Y is CR^{3a} , Z and V can not both be N;
 (G) when Z is CR^2 , V and Y must both be N;
 25 (H) Z can be N only when both V and Y are N or when V is CR^{1a} and Y is CR^{3a} ;
 (I) when V and Y are N, Z is CR^2 , and R^2 is H or C_1 - C_3 alkyl, and R^4 is C_1 - C_3
 alkyl, R^3 can not be 2-pyridinyl, indolyl, indolinyl, imidazolyl, 3-pyridinyl, 4-pyridinyl,
 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, furanyl, 5-methyl-2-furanyl,
 2,5-dimethyl-3-furanyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, or
 30 4-pyrazinyl;
 (J) when V and Y are N; Z is CR^2 ; R^2 is H or C_1 - C_3 alkyl; R^4 is C_1 - C_4 alkyl, R^5 , X,
 and/or X' are OH, halo, CF_3 , C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, cyano, amino,
 carbamoyl, or C_1 - C_4 alkanoyl; and R^1 is C_1 - C_4 alkyl, then R^4 can not be
 $-NH$ (substituted phenyl) or $-N(C_1-C_4 \text{ alkyl})$ (substituted phenyl);

and wherein, when Y is CR²⁹:

J, K, L, M, Z, A, k, m, n, p, q, r, t, w, R³, R¹⁰, R¹¹, R¹², R¹³, R¹⁶, R¹⁸, R¹⁹, R²¹, R²³, R²⁴, R²⁵, and R²⁷ are as defined above and R^{25a}, in addition to being as defined above, can also be C₁-C₄ alkyl, but

5 V is N;

R¹ is C₁-C₂ alkyl, C₂-C₄ alkenyl, C₂-C₄ alkynyl, C₂-C₄ alkoxy, halogen, amino, methylamino, dimethylamino, aminomethyl, or N-methylaminomethyl;

R² is independently selected at each occurrence from the group consisting of hydrogen, halo, C₁-C₃, alkyl, nitro, amino, and -CO₂R¹⁰;

10 R₄ is taken together with R²⁹ to form a 5-membered ring and is -C(R²⁶) = or -N= when R²⁹ is -C(R³⁰)= or -N=, or -CH(R²⁶)- when R²⁹ is -CH(R³⁰)-;

X is Cl, Br, I, S(O)_nR⁸, OR⁸, halomethyl, -(CHR¹⁶)_pOR⁸, cyano, -(CHR¹⁶)_pNR¹⁴R¹⁵, C(=O)R⁸, C₁-C₆ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀, alkoxy, aryl-(C₁-C₁₀)-alkyl, C₃-C₆ cycloalkyl, aryl-(C₁-C₁₀)-alkoxy, nitro, 15 thio-(C₁-C₁₀)-alkyl, -C(=NOR¹⁶)-C₁-C₄-alkyl, -C(=NOR¹⁶)H, or C(=O)NR¹⁴R¹⁵ where substitution by R¹⁸ can occur on any carbon containing substituents;

X' is hydrogen, Cl, Br, I, S(O)_nR⁸, -(CHR¹⁶)_pOR⁸, halomethyl, cyano, -(CHR¹⁶)_pNR¹⁴R¹⁵, C(=O)R⁸, C₁-C₆ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₁-C₁₀ alkoxy, aryl-(C₁-C₁₀)-alkyl, C₃-C₆ cycloalkyl, aryl-(C₂-C₁₀)-alkoxy, nitro, thio-(C₂-C₁₀)-alkyl, 20 -C(=NOR¹⁶)-C₁-C₄-alkyl, -C(=NOR¹⁶)H, or C(=O)NR⁸R¹⁵ where substitution by R¹⁸ can occur on any carbon containing substituents;

R⁵ is halo, -C(=NOR¹⁶)-C₁-C₄-alkyl, C₁-C₆ alkyl, C₁-C₃ haloalkyl, C₁-C₆ alkoxy, (CHR¹⁶)_pOR⁵, (CHR¹⁶)_pS(O)_nR⁸, (CHR¹⁶)_pNR¹⁴R¹⁵, C₃-C₆ cycloalkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, aryl-(C₂-C₁₀)-alkyl, aryl-(C₁-C₁₀)-alkoxy, cyano, C₃-C₆ cycloalkoxy, 25 nitro, amino-(C₁-C₁₀)-alkyl, thio-(C₁-C₁₀)-alkyl, SO_n(R⁸), C(=O)R⁸, -C(=NOR¹⁶)H, or C(=O)NR⁸R¹⁵ where substitution by R¹⁸ can occur on any carbon containing substituents;

R⁶ and R⁷ are independently selected at each occurrence from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₁₀ cycloalkyl, -(CH₂)_kR¹³, 30 (C₄-C₁₂)-cycloalkylalkyl, C₁-C₆ alkoxy, -(C₁-C₆ alkyl)-aryl, heteroaryl, aryl, -S(O)_z-aryl or -(C₁-C₆ alkyl)-heteroaryl or aryl wherein the aryl or heteroaryl groups are optionally substituted with 1-3 groups selected from hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino, NHC(=O)(C₁-C₆ alkyl), NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, nitro, carboxy, CO₂(C₁-C₆ alkyl), and cyano; or can be taken together to form -(CH₂)_qA(CH₂)_r-,

optionally substituted with 0-3 R^{17} ; or, when considered with the commonly attached nitrogen, can be taken together to form a heterocycle, said heterocycle being substituted on carbon with 1-3 groups consisting of hydrogen, C_1 - C_6 alkyl, hydroxy, or C_1 - C_6 alkoxy;

- 5 R^8 is independently selected at each occurrence from the group consisting of hydrogen, C_1 - C_6 alkyl, $-(C_4-C_{12})$ cycloalkylalkyl, $(CH_2)_i R^{22}$, C_3 - C_{10} cycloalkyl, $-(C_1-C_6$ alkyl)-aryl, heteroaryl, $-NR^{16}$, $-N(CH_2)_n NR^6 R^7$; $-(CH_2)_k R^{25}$, $-(C_1-C_6$ alkyl)-heteroaryl or aryl optionally substituted with 1-3 groups selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, amino, $NHC(=O)(C_1-C_6$ alkyl), $NH(C_1-C_6$ alkyl), $N(C_1-C_6$ alkyl) $_2$,
10 nitro, carboxy, $CO_2(C_1-C_6$ alkyl), and cyano;

R^9 is independently selected at each occurrence from R^{10} , hydroxy, C_1 - C_4 alkoxy, C_3 - C_6 cycloalkyl, C_2 - C_4 alkenyl, and aryl substituted with 0-3 R^{18} ;

- R^{14} and R^{15} are independently selected at each occurrence from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, $(CH_2)_i R^{22}$, and aryl substituted
15 with 0-3 R^{18} ;

R^{17} is independently selected at each occurrence from the group consisting of R^{10} , C_1 - C_4 alkoxy, halo, OR^{23} , SR^{23} , and $NR^{23} R^{24}$;

R^{20} is independently selected at each occurrence from the group consisting of R^{10} and $C(=O)R^{31}$;

- 20 R^{22} is independently selected at each occurrence from the group consisting of cyano, OR^{24} , SR^{24} , $NR^{23} R^{24}$, C_3 - C_6 cycloalkyl, $-S(O)_n R^{31}$, and $-C(=O)R^{25}$;

R^{26} is hydrogen or halogen;

R^{28} is C_1 - C_2 , alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, hydrogen, C_1 - C_2 alkoxy, halogen, or C_2 - C_4 alkylamino;

- 25 R^{29} is taken together with R^4 to form a five membered ring and is: $-CH(R^{30})-$ when R^4 is $-CH(R^{28})-$, $-C(R^{30})=$ or $-N=$ when R^4 is $-C(R^{28})=$ or $-N=$;

R^{30} is hydrogen, cyano, C_1 - C_2 alkyl, C_1 - C_2 alkoxy, halogen, C_1 - C_2 alkenyl, nitro, amido, carboxy, or amino;

- 30 R^{31} is C_1 - C_4 alkyl, C_3 - C_7 cycloalkyl, or aryl- (C_1-C_4) alkyl; provided that when J, K, and L are all CH, M is CR^5 , Z is CH, R^3 is CH_3 , R^{28} is H, R^5 is isopropyl, X is Br, X' is H, and R^1 is CH_3 , then R^{30} can not be H, $-CO_2H$, or $-CH_2NH_2$; and further provided that when J, K and L are all CH; M is CR^5 ; Z is N; and

(A) R^{29} is $-C(R^{30})=$; then one of R^{28} or R^{30} is hydrogen;

(B) R^{29} is N; then R^3 is not halo, NH_2 , NO_2 , CF_3 , CO_2H , CO_2 -alkyl, alkyl, acyl, alkoxy, OH, or $-(CH_2)_mOalkyl$;

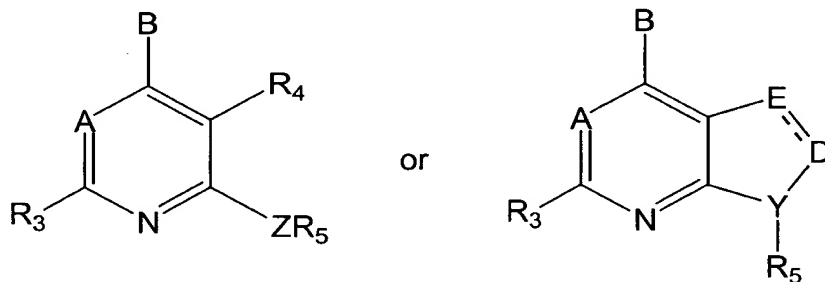
(C) R^{29} is N; then R^{28} is not methyl if X or X' are bromo or methyl and R^5 is nitro; or

5 (D) R^{29} is N; and R^1 is CH_3 ; and R^3 is amino; then R^5 is not halogen or methyl.

Preferred compounds of this group include those wherein:

- i) V is N, R^1 is methyl; and R^3 is aryl, NR^6R^7 , or OR^8 ;
- ii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7 , or OR^8 ; and R^4 is methyl or ethyl;
- 10 iii) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7 , or OR^8 ; R^4 is methyl or ethyl; and X is $O(C_1-C_4 alkyl)$, Br, or $C_1-C_4 alkyl$;
- iv) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7 , or OR^8 ; R^4 is methyl, ethyl; X is OMe, Br, or $(C_1-C_4 alkyl)$, M is $C_1-C_4 alkyl$, Br, Cl, or $O(C_1-C_4 alkyl)$; and
- v) V is N, R^1 is methyl; R^3 is aryl, NR^6R^7 , OR^8 ; or R^4 is methyl, ethyl; X is
- 15 OMe, Br, or $C_1-C_4 alkyl$, M is $C_1-C_4 alkyl$, Br, Cl, or $O(C_1-C_4 alkyl)$; and L is CH, or N.

Another group of useful CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound of the following formula, disclosed in EP 0773023:



20

or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;

A is $-CR_7$ or N;

25 B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_1R_{12})R_2$, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNH_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;

D is N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$;

-CR₁₀ when a double bond connects E and D and E is N; or -CR₈R₉, -CHR₁₀, -C=O, -C=S, -C=NH, or -C=NCH₃ when a single bond connects E and D;

E is -CR₄ or N when a double bond connects E and D, and E is -CR₄R₆ or -NR₆ when a single bond connects E and D;

5 Y is N or -CH;

Z is NH, O, S, -N(C₁-C₂ alkyl), or -CR₁₂R₁₃, wherein R₁₂ and R₁₃ are each, independently, hydrogen, trifluoromethyl, or methyl, or one of R₁₂ and R₁₃ is cyano and the other is hydrogen or methyl;

R₁ is hydrogen or C₁-C₆ alkyl which is optionally substituted with up to two
10 substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF₃, C₁-C₄ alkoxy, -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -CO₂(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), (C₁-C₄ alkyl)sulfinyl, (C₁-C₄ alkyl)sulfonyl, and
15 (C₁-C₄ alkyl)sulfanyl, and wherein said C₁-C₆ alkyl, C₁-C₄ alkoxy, and C₁-C₄ alkyl moieties in the foregoing R₁ groups optionally contain one double or triple bond;

R₂ is C₁-C₆ alkyl, heteroaryl, aryl, heteroaryl (C₁-C₄ alkyl), or aryl (C₁-C₄ alkyl), wherein said aryl and the aryl moiety of said (aryl)C₁-C₄ alkyl are selected from the group consisting of phenyl and naphthyl, and said heteroaryl and the heteroaryl
20 moiety of said (heteroaryl)C₁-C₄ alkyl is selected from the group consisting of thienyl, benzothienyl, pyridyl, thiazolyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R² is C₃-C₈ cycloalkyl or (C₃-C₈ cycloalkyl)C₁-C₆ alkyl, wherein one or two of the ring carbons of said cycloalkyl having
25 at least 4 ring members and the cycloalkyl moiety of said (C₃-C₈ cycloalkyl)C₁-C₆ alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by -NR₁₄ wherein R₁₄ is hydrogen or C₁-C₄ alkyl; and wherein each of the foregoing R₂ groups is optionally substituted by up to three substituents independently selected from chloro, fluoro, and C₁-C₄ alkyl, or by one substituent selected from bromo, iodo,
30 cyano, nitro, C₁-C₆ alkoxy, -O-CO-(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -CO₂(C₁-C₄ alkyl), (C₁-C₄ alkyl)sulfanyl, (C₁-C₄ alkyl)sulfinyl, and (C₁-C₄ alkyl)sulfonyl, and wherein said C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₂ groups optionally contain one carbon-carbon double or triple bond;

or R¹ and R² of said -NR₁R₂ and said -CR₁R₂R₁₁ are taken together to form a saturated or partially saturated 5- to 8-membered ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by a heteroatom selected from O, S, and N;

5 R₃ is hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -CH₂OH, -CH₂OCH₃, -O(C₁-C₄ alkyl), (C₁-C₄ alkyl)sulfanyl, (C₁-C₄ alkyl)sulfonyl, or (C₁-C₄ alkyl)sulfinyl, wherein said C₁-C₆ alkyl and C₁-C₄ alkyl moieties of the foregoing R₃ groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents
10 independently selected from hydroxy, amino, C₁-C₃ alkoxy, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -NHCOCH₃, fluoro, chloro, and C₁-C₃ thioalkyl;

R₄ is hydrogen, C₁-C₆ alkyl, fluoro, chloro, bromo, iodo, C₁-C₆ alkoxy, formyl, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂CF₃, CF₃, amino, nitro, -NH(C₁-C₄ alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, (C₁-C₄ alkyl)sulfanyl, (C₁-C₄ alkyl)sulfinyl, (C₁-C₄ alkyl)sulfonyl, cyano, hydroxy, -CO(C₁-C₄ alkyl), -CHO, or
15 -CO₂(C₁-C₄ alkyl), wherein said C₁-C₆ alkyl, C₁-C₆ alkoxy, and C₁-C₄ alkyl moieties of the foregoing R₄ groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)₂, -CO₂(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), C₁-C₃ alkoxy, (C₁-C₃ alkyl)sulfanyl, fluoro, chloro, cyano, and nitro;
20

R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or a 3- to 8-membered cycloalkyl ring or a 9- to 12-
25 membered bicycloalkyl ring system, wherein said cycloalkyl ring and said bicycloalkyl ring system optionally contain one or two of O, S, or -N-G wherein G is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkanoyl, phenyl, or benzyl, wherein each of the above R₅ groups is optionally substituted by up to three substituents independently selected from fluoro, chloro, C₁-C₆ alkyl, C₁-C₆ alkoxy, and trifluoromethyl, or one substituent selected from
30 bromo, iodo, cyano, nitro, amino, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -CO₂(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), wherein said C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₅ groups optionally contain

one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino, and acetyl;

5 R_6 is hydrogen or C_1 - C_6 alkyl, wherein said C_1 - C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy, or fluoro group;

R_7 is hydrogen, C_1 - C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1 - C_4 alkoxy, $-CO(C_1$ - C_4 alkyl), $-CO_2(C_1$ - C_4 alkyl), $-OCF_3$, CF_3 , $-CH_2OH$, $-CH_2OCH_3$, or $-CH_2OCH_2CH_3$;

10 R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy;
or R_8 and R_9 together form an oxo ($=O$) group;

R_{10} is hydrogen, C_1 - C_6 alkyl, fluoro, chloro, bromo, iodo, C_1 - C_6 alkoxy, formyl, amino, $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), cyano, carboxy, amido, or $-SO_n(C_1$ - C_4 alkyl) wherein n is 0, 1, or 2, wherein said C_1 - C_6 alkyl and C_1 - C_4 alkyl
15 moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, $-NHCO(C_1$ - C_4 alkyl), $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), $-CO_2(C_1$ - C_4 alkyl), C_1 - C_3 alkoxy, C_1 - C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano, or nitro; and

20 R_{11} is hydrogen, hydroxy, fluoro, or methoxy.

Another group of preferred CRF antagonists for use in the compositions, methods, and kits of the present invention are those wherein the CRF antagonist is a compound selected from the group consisting of:

25 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-
d]pyrimidin-4-yl]-amino}-propan-1-ol;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-
30 d]pyrimidin-4-yl]-amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-
d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-
d]pyrimidin-4-yl]amino}-ethanol;

- [3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
- 4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
- 5 2,5,6-trimethyl-7-(1-propylbutyl)-4-(2,4,6-trimethylphenoxy)-7H-pyrrolo[2,3-d]pyrimidine;
- 1-(1-ethylpropyl)-6-methyl-4-(2,4,6-trimethylphenoxy)-1,3-dihydro-imidazo[4,5-c]pyridin-2-one;
- 1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-10 2H-pyrido[3,4-b]pyrazin-3-one;
- 1-(1-ethyl-propyl)-4,7-dimethyl-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-pyrido[3,4-b]pyrazine;
- 1-(1-ethyl-propyl)-7-methyl-2-oxo-5-(2,4,6-trimethyl-phenoxy)-1,2,3,4-tetrahydro-[1,6]naphthyridine-3-carboxylic acid isopropyl ester;
- 15 1-(1-ethyl-propyl)-7-methyl-5-(2,4,6-trimethyl-phenoxy)-1,4-dihydro-2H-3-oxa-1,6-diaza-naphthalene;
- (1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-amine;
- 7-(1-ethyl-propoxy)-2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-pyrazolo[1,5-a]pyrimidine;
- 20 4-(1-ethyl-propoxy)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5H-pyrrolo[3,2-d]pyrimidine;
- 4-(butyl-ethyl-amino)-2,6-dimethyl-8-(2,4,6-trimethyl-phenyl)-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one;
- 25 8-(1-ethyl-propoxy)-6-methyl-4-(2,4,6-trimethyl-phenyl)-1,2,3,4-tetrahydro-pyrido [2,3-b]pyrazine;
- 4-(1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;
- (1-ethyl-propyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-quinolin-4-yl]-amine;
- (propyl-ethyl)-[2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido-30 [2,3-d] pyrimidin-4-yl]-amine;
- (1-ethyl-propoxy)-2-methyl-8-(2,4,6-trimethyl-phenyl)-5,6,7,8-tetrahydro-pyrido[2,3-d] pyrimidine;
- 8-(1-hydroxymethyl-propylamino)-6-methyl-4-(2,4,6-trimethyl-phenyl)-3,4-dihydro-1H-pyrido[2,3-b]pyrazin-2-one;

4-(1-hydroxymethyl-propylamino)-2-methyl-8-(2,4,6-trimethyl-phenyl)-quinoline;

5-(1-hydroxymethyl-propylamino)-7-methyl-1-(2,4,6-trimethyl-phenyl)-1,4-dihydro-2H-3-oxa-1,8-diaza-naphthalene;

5 [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
cyclopropylmethyl-[3-(2,4-dimethyl-phenyl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl]-propyl-amine;

[2,5-dimethyl-3-(2,4-dimethyl-phenyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-(1-ethyl-propyl)-amine;

10 3-[6-(dimethylamino)-3-pyridinyl-2,5-dimethyl-N,N-dipropylpyrazolo[2,3-a]pyrimidin-7-amine;

3-[6-(dimethylamino)-4-methyl-3-pyridinyl]-2,5-dimethyl-N,N-dipropyl-pyrazolo[2,3-a]pyrimidine-7-amine;

15 3-(2,4-dimethoxyphenyl)-2,5-dimethyl-7-(N-propyl-N-methoxyethylamino)-pyrazolo(2,3-a)pyrimidine;

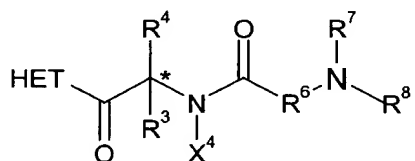
7-(N-diethylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]-pyrazolopyrimidine; and

7-(N-(3-cyanopropyl)-N-propylamino-2,5-dimethyl-3-(2,4-dimethylphenyl)-[1,5-a]-pyrazolopyrimidine.

20

A group of preferred growth hormones or growth hormone secretagogues for use in the compositions, methods, and kits of the present invention are those wherein the growth hormone or growth hormone secretagogue is a growth hormone.

25 A group of preferred growth hormone secretagogues for use in the compositions, methods, and kits of the present invention are those wherein the growth hormone secretagogue is a compound of formula IV:

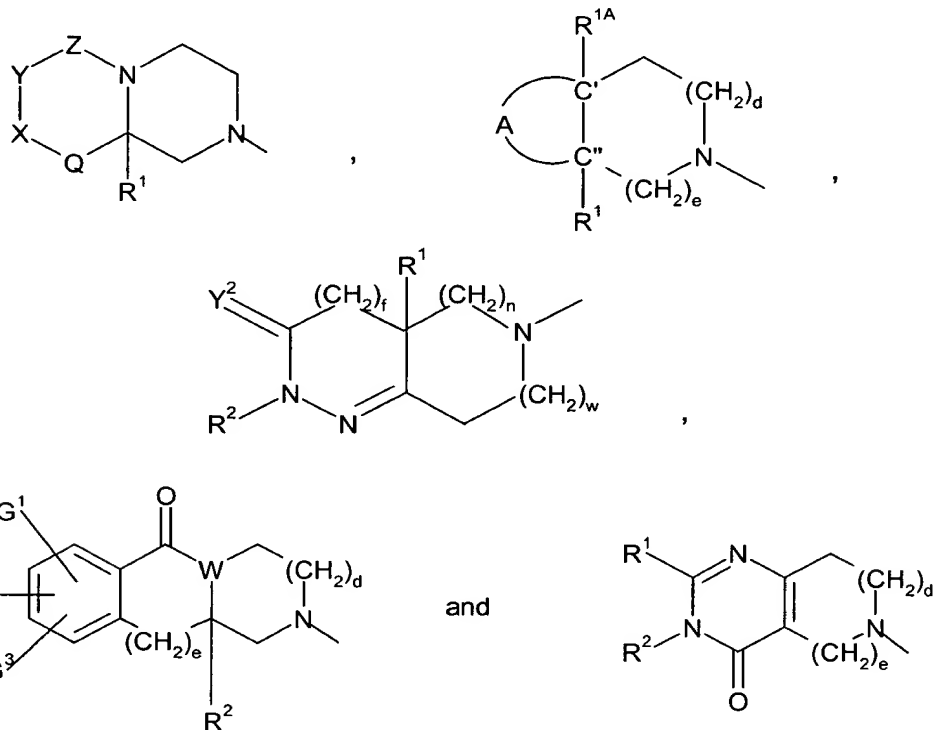


IV

30 or a stereoisomeric mixture thereof, a diastereomerically enriched, diastereomerically pure, enantiomerically enriched, or enantiomerically pure isomer thereof, or a prodrug

of such compound, mixture, or isomer thereof, or a pharmaceutically acceptable salt of the compound, mixture, isomer, or prodrug, wherein:

HET is a heterocyclic moiety selected from the group consisting of



5 d is 0, 1, or 2;

e is 1 or 2;

f is 0 or 1;

n and w are 0, 1, or 2, provided that n and w cannot both be 0 at the same time;

10 Y² is oxygen or sulfur;

A is a divalent radical, wherein the left hand side of the radical as shown below is connected to C' and the right hand side of the radical as shown below is connected to C'', selected from the group consisting of -NR²-CO-NR²-, -NR²-SO₂-NR²-, -O-CO-NR²-, -NR²-CO₂-, -CO-NR²-CO-, -CO-NR²-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-NR²-CO-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -SO₂-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-O-CO-, -C(R⁹R¹⁰)-O-C(R⁹R¹⁰)-, -NR²-CO-C(R⁹R¹⁰)-, -O-CO-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-CO-NR²-, -CO-NR²-CO-, -C(R⁹R¹⁰)-CO₂-, -CO-NR²-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -CO₂-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -SO₂-NR²-C(R⁹R¹⁰)-C(R⁹R¹⁰)-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-NR²-CO-, -C(R⁹R¹⁰)-C(R⁹R¹⁰)-O-CO-, -NR²-CO-

$C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-SO_2-C(R^9R^{10})-C(R^9R^{10})-$, $-O-CO-C(R^9R^{10})-C(R^9R^{10})-$,
 $-C(R^9R^{10})-C(R^9R^{10})-CO-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-CO-$, $-C(R^9R^{10})-NR^2-CO_2-$,
 $-C(R^9R^{10})-O-CO-NR^2$, $-C(R^9R^{10})-NR^2-CO-NR^2-$, $-NR^2-CO_2-C(R^9R^{10})-$, $-NR^2-CO-NR^2-$
 $C(R^9R^{10})-$, $-NR^2-SO_2-NR^2-C(R^9R^{10})-$, $-O-CO-NR^2-C(R^9R^{10})-$, $-CO-N=C(R^{11})-NR^2-$,
5 $-CO-NR^2-C(R^{11})=N-$, $-C(R^9R^{10})-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$, $-NR^{12}-C(R^9R^{10})-$
 $C(R^9R^{10})-$, $-CO_2-C(R^9R^{10})-C(R^9R^{10})-$, $-NR^2-C(R^{11})=N-CO-$, $-C(R^9R^{10})-C(R^9R^{10})-N(R^{12})-$,
 $-C(R^9R^{10})-NR^{12}-$, $-N=C(R^{11})-NR^2-CO-$, $-C(R^9R^{10})-C(R^9R^{10})-NR^2-SO_2-$, $-C(R^9R^{10})-$
 $C(R^9R^{10})-SO_2-NR^2-$, $-C(R^9R^{10})-C(R^9R^{10})-CO_2-$, $-C(R^9R^{10})-SO_2-C(R^9R^{10})-$, $-C(R^9R^{10})-$
 $C(R^9R^{10})-SO_2-$, $-O-C(R^9R^{10})-C(R^9R^{10})-$, $-C(R^9R^{10})-C(R^9R^{10})-O-$, $-C(R^9R^{10})-CO-$
10 $C(R^9R^{10})-$, $-CO-C(R^9R^{10})-C(R^9R^{10})-$, and $-C(R^9R^{10})-NR^2-SO_2-NR^2-$;

Q is a covalent bond or CH_2 ;

W is CH or N;

X is CR^9R^{10} , $C=CH_2$, or $C=O$;

Y is CR^9R^{10} , O, or NR^2 ;

15 Z is $C=O$, $C=S$, or SO_2 ;

G^1 is hydrogen, halo, hydroxy, nitro, amino, cyano, phenyl, carboxyl, $-CONH_2$,
 $-C_1-C_4$ alkyl optionally independently substituted with one or more phenyl, one or
more halogen, or one or more hydroxy groups, $-C_1-C_4$ alkoxy optionally independently
substituted with one or more phenyl, one or more halogen, or one or more hydroxy
20 groups, $-C_1-C_4$ alkylthio, phenoxy, $-CO_2-(C_1-C_4$ alkyl), N,N-di-(C_1-C_4 alkylamino), $-C_2-$
 C_6 alkenyl optionally independently substituted with one or more phenyl, one or more
halogen, or one or more hydroxy groups, $-C_2-C_6$ alkynyl optionally independently
substituted with one or more phenyl, one or more halogen, or one or more hydroxy
groups, $-C_3-C_6$ cycloalkyl optionally independently substituted with one or more C_1-C_4
25 alkyl groups, one or more halogen, or one or more hydroxy groups, $-C_1-C_4$ alkylamino
carbonyl, or di- C_1-C_4 alkylamino) carbonyl;

G^2 and G^3 are each independently selected from the group consisting of
hydrogen, halo, hydroxy, $-C_1-C_4$ alkyl optionally independently substituted with one to
three halo groups, and $-C_1-C_4$ alkoxy optionally independently substituted with one to
30 three halo groups;

R^1 is hydrogen, $-CN$, $-(CH_2)_qNX^6COX^6$, $-(CH_2)_qNX^6CO(CH_2)_tA^1$,
 $-(CH_2)_qNX^6SO_2(CH_2)_tA^1$, $-(CH_2)_qNX^6SO_2X^6$, $-(CH_2)_qNX^6CONX^6(CH_2)_tA^1$,
 $-(CH_2)_qNX^6CONX^6X^6$, $-(CH_2)_qCONX^6X^6$, $-(CH_2)_qCONX^6(CH_2)_tA^1$, $-(CH_2)_qCO_2X^6$,
 $-(CH_2)_qCO_2(CH_2)_tA^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOCOX^6$, $-(CH_2)_qOCO(CH_2)_tA^1$,

$-(CH_2)_qOCONX^6(CH_2)_tA^1$, $-(CH_2)_qOCONX^6X^6$, $-(CH_2)_qCOX^6$, $-(CH_2)_qCO(CH_2)_tA^1$,
 $-(CH_2)_qNX^6CO_2X^6$, $-(CH_2)_qNX^6SO_2NX^6X^6$, $-(CH_2)_qSO_mX^6$, $-(CH_2)_qSO_m(CH_2)_tA^1$,
 $-C_1-C_{10}$ alkyl, $-(CH_2)_tA^1$, $-(CH_2)_q-(C_3-C_7$ cycloalkyl), $-(CH_2)_q-Y^1-(C_1-C_6$ alkyl), $-(CH_2)_q-$
 $Y^1-(CH_2)_tA^1$, or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7$ cycloalkyl);

5 wherein the alkyl and cycloalkyl groups in the definition of R^1 are
optionally substituted with C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, carboxyl, -
 $CONH_2$, $-SO_m-(C_1-C_6$ alkyl), $-CO_2-(C_1-C_4$ alkyl) ester, 1H-tetrazol-5-yl, or 1, 2,
or 3 fluoro groups;

Y^1 is O, SO_m , $-CONX^6-$, $-CH=CH-$, $-C\equiv C-$, $-NX^6CO-$, $-CONX^6-$, $-CO_2-$,
10 $-OCONX^6-$ or $-OCO-$;

 q is 0, 1, 2, 3, or 4;

 t is 0, 1, 2, or 3;

 said $(CH_2)_q$ group and $(CH_2)_t$ group in the definition of R^1 are optionally
independently substituted with hydroxy, C_1-C_4 alkoxy, carboxyl, $-CONH_2$, -
15 $SO_m-(C_1-C_6$ alkyl), $-CO_2-(C_1-C_4$ alkyl) ester, 1H-tetrazol-5-yl, 1, 2, or 3 fluoro
groups, or 1 or 2 C_1-C_4 alkyl groups;

R^{1A} is selected from the group consisting of hydrogen, F, Cl, Br, I, C_1-C_6 alkyl,
phenyl- $(C_1-C_3$ alkyl), pyridyl- $(C_1-C_3$ alkyl), thiazolyl- $(C_1-C_3$ alkyl), and thienyl- $(C_1-C_3$
alkyl), provided that R^{1A} is not F, Cl, Br, or I when a heteroatom is vicinal to C";

20 R^2 is hydrogen, C_1-C_8 alkyl, $-(C_0-C_3$ alkyl)- $(C_3-C_8$ cycloalkyl), $-(C_1-C_4$ alkyl)- A^1 ,
or A^1 , wherein the alkyl groups and the cycloalkyl groups in the definition of R^2 are
optionally substituted with hydroxy, $-CO_2X^6$, $-CONX^6X^6$, $-NX^6X^6$, $-SO_m(C_1-C_6$ alkyl), -
 COA^1 , $-COX^6$, CF_3 , CN, or 1, 2, or 3 independently selected halo groups;

R^3 is selected from the group consisting of A^1 , C_1-C_{10} alkyl, $-(C_1-C_6$ alkyl)- A^1 , -
25 $(C_1-C_6$ alkyl)- $(C_3-C_7$ cycloalkyl), $-(C_1-C_5$ alkyl)- $X^1-(C_1-C_5$ alkyl), $-(C_1-C_5$ alkyl)- $X^1-(C_0-C_5$
alkyl)- A^1 , and $-(C_1-C_5$ alkyl)- $X^1-(C_1-C_5$ alkyl)- $(C_3-C_7$ cycloalkyl);

 wherein the alkyl groups in the definition of R^3 are optionally
substituted with $-SO_m(C_1-C_6$ alkyl), $-CO_2X^3$, 1, 2, 3, 4, or 5 independently
selected halo groups, or 1, 2, or 3 independently selected $-OX^3$ groups;

30 X^1 is O, SO_m , $-NX^2CO-$, $-CONX^2-$, $-OCO-$, $-CO_2-$, $-CX^2=CX^2-$,
 $-NX^2CO_2-$, $-OCONX^2-$, or $-C\equiv C-$;

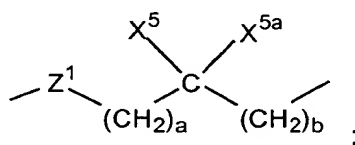
R^4 is hydrogen, C_1-C_6 alkyl, or C_3-C_7 cycloalkyl, or R^4 taken together with R^3
and the carbon atom to which they are attached form C_5-C_7 cycloalkyl, C_5-C_7
cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to

4 heteroatoms independently selected from the group consisting of oxygen, sulfur, and nitrogen, or a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated, or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms

5 independently selected from the group consisting of nitrogen, sulfur, and oxygen;

X^4 is hydrogen or C_1-C_6 alkyl, or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

R^6 is a bond or is



wherein a and b are each independently 0, 1, 2, or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, CF_3 , A^1 , and C_1-C_6 alkyl optionally substituted with A^1 , OX^2 , -
15 $SO_m-(C_1-C_6 \text{ alkyl})$, $-CO_2X^2$, C_3-C_7 cycloalkyl, $-NX^2X^2$, or $-CONX^2X^2$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then only one of X^5 or X^{5a} is on the carbon atom and only one of R^7 or R^8 is on the
20 nitrogen atom, and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 taken together with X^{5a} and the carbon atom to which they are attached form a partially saturated or fully saturated 3- to 7-membered ring, or
25 a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur, and nitrogen;

or X^5 taken together with X^{5a} and the carbon atom to which they are attached form a bicyclic ring system consisting of a partially saturated or fully
30 saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur, and

oxygen, fused to a partially saturated, fully saturated, or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur, and oxygen;

Z^1 is a bond, O, or $N-X^2$, provided that when a and b are both 0 then

5 Z^1 is not $N-X^2$ or O;

R^7 and R^8 are each independently hydrogen or C_1-C_6 alkyl optionally independently substituted with A^1 , $-CO_2-(C_1-C_6 \text{ alkyl})$, $-SO_m(C_1-C_6 \text{ alkyl})$, 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 $-O-CO(C_1-C_{10} \text{ alkyl})$ groups, or 1 to 3 C_1-C_6 alkoxy groups; or

10 R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$, wherein L is CX^2X^2 , SO_m , or NX^2 ;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, fluoro, hydroxy, and C_1-C_5 alkyl optionally independently substituted with 1-5 halo groups;

15 R^{11} is selected from the group consisting of C_1-C_5 alkyl and phenyl optionally substituted with 1-3 substituents each independently selected from the group consisting of C_1-C_5 alkyl, halo, and C_1-C_5 alkoxy;

R^{12} is selected from the group consisting of C_1-C_5 alkylsulfonyl, C_1-C_5 alkanoyl, and C_1-C_5 alkyl wherein the alkyl portion is optionally independently substituted by 1-5 halo groups;

20 A^1 for each occurrence is independently selected from the group consisting of C_5-C_7 cycloalkenyl, phenyl, a partially saturated, fully saturated, or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur, and nitrogen, and a bicyclic ring system consisting of a partially saturated, fully unsaturated, or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur, and oxygen, fused to a partially saturated, fully saturated, or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur, and oxygen;

30 A^1 for each occurrence is independently optionally substituted, on one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-CONX^6X^6$, -

CO₂X⁶, oxo, C₁-C₆ alkyl, nitro, cyano, benzyl, -SO_m(C₁-C₆ alkyl), 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -NX⁶X⁶, -NX⁶COX⁶, -SO₂NX⁶X⁶, -NX⁶SO₂-phenyl, NX⁶SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶COX¹²,
 5 imidazolyl, thiazolyl, and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

wherein X¹¹ is hydrogen or C₁-C₆ alkyl optionally independently substituted with phenyl, phenoxy, C₁-C₆ alkoxy carbonyl, -SO_m(C₁-C₆ alkyl), 1 to 5 halo groups, 1 to 3 hydroxy groups, 1 to 3 C₁-C₁₀ alkanoyloxy groups, or 1 to 3 C₁-C₆ alkoxy groups;
 10

X¹² is hydrogen, C₁-C₆ alkyl, phenyl, thiazolyl, imidazolyl, furyl, or thienyl, provided that when X¹² is not hydrogen, the X¹² group is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃, and CF₃;
 15

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r, wherein L¹ is CX²X², O, SO_m, or NX²;

r for each occurrence is independently 1, 2, or 3;

X² for each occurrence is independently hydrogen, optionally substituted C₁-C₆ alkyl, or optionally substituted C₃-C₇ cycloalkyl, wherein the optionally substituted C₁-C₆ alkyl and optionally substituted C₃-C₇ cycloalkyl in the definition of X² are optionally independently substituted with -SO_m(C₁-C₆ alkyl), -CO₂X³, 1 to 5 halo groups, or 1-3 OX³ groups;
 20

X³ for each occurrence is independently hydrogen or C₁-C₆ alkyl;

X⁶ for each occurrence is independently hydrogen, optionally substituted C₁-C₆ alkyl, halogenated C₂-C₆ alkyl, optionally substituted C₃-C₇ cycloalkyl, halogenated C₃-C₇ cycloalkyl, wherein the optionally substituted C₁-C₆ alkyl and optionally substituted C₃-C₇ cycloalkyl in the definition of X⁶ are optionally independently mono- or di-substituted with C₁-C₄ alkyl, hydroxy, C₁-C₄ alkoxy, carboxyl, CONH₂, -SO_m(C₁-C₆ alkyl), carboxylate (C₁-C₄ alkyl) ester, or 1H-tetrazol-5-yl; or
 25
 30

when there are two X⁶ groups on one atom and both X⁶ are independently C₁-C₆ alkyl, the two C₁-C₆ alkyl groups may be optionally joined, and together with the atom to which the two X⁶ groups are attached, form a 4- to 9- membered ring

optionally having oxygen, sulfur, or NX^7 as a ring member, wherein X^7 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl optionally substituted with hydroxy;

m for each occurrence is independently 0, 1, or 2;

with the provisos that:

- 5 X^6 and X^{12} cannot be hydrogen when attached to CO or SO_2 in the form COX^6 , COX^{12} , SO_2X^6 or SO_2X^{12} ; and

when R^6 is a bond then L is NX^2 and each r in the definition $-(\text{CH}_2)_r\text{-L-(CH}_2)_r\text{-}$ is independently 2 or 3.

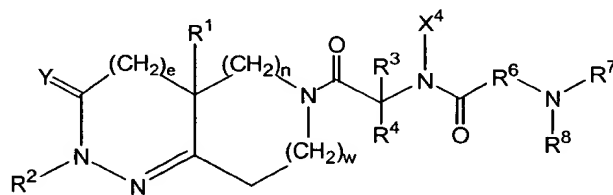
- Another group of preferred growth hormone secretagogues for use in the
10 compositions, methods, and kits of the present invention are those wherein the growth hormone secretagogue is 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide; 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-
15 pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide; 2-amino-N-{1(R)-benzyloxymethyl-2-[1,3-dioxo-8a(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-hexahydro-imidazo[1,5-a]pyrazin-7-yl]-2-oxo-ethyl}-2-methyl-propionamide; N-(1(R)-((1,2-dihydro-1-methanesulfonyl-spiro(3H-indole-3,4'-piperidin)-1'-yl)carbonyl)-2-(phenylmethoxy)ethyl)-2-amino-2-methyl-propanamide; or a prodrug of any of these
20 compounds, or a pharmaceutically acceptable salt of any of said compounds or said prodrugs.

DETAILED DESCRIPTION OF THE INVENTION

- 25 The present invention is directed to pharmaceutical compositions, methods, and kits comprising a CRF antagonist and a growth hormone secretagogue or growth hormone useful for treating a wide variety of diseases and conditions as fully described herein. While many specific compounds that serve as CRF antagonists, growth hormones, or growth hormone secretagogues are described and discussed
30 herein, all such compounds, either cited herein or not, presently known or yet to be discovered, are considered to be useful in the practice of the present invention.

The second component of the compositions, methods, and kits of the present invention is a growth hormone secretagogue or growth hormone *per se*.

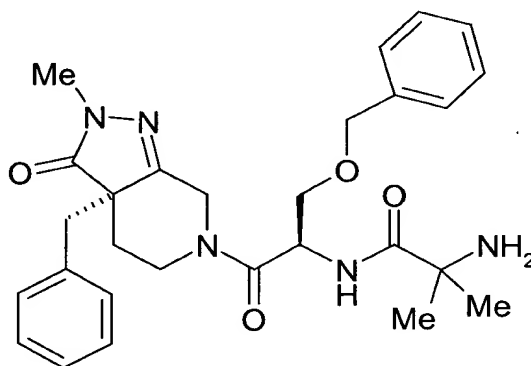
A representative first class of growth hormone secretagogues is set forth in PCT publication WO 97/24369, which is incorporated herein by reference, as compounds having the formula III:



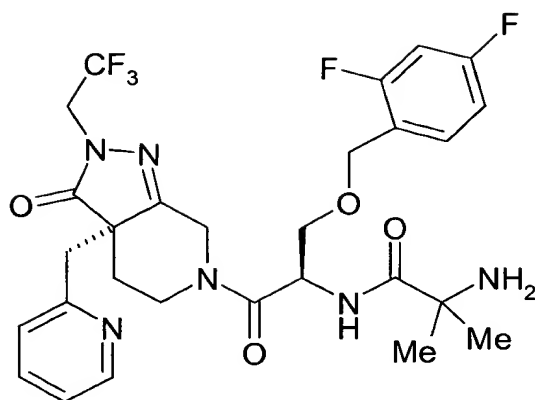
III

- 5 wherein the various substituents are as defined in WO 97/24369. Said compounds are prepared as disclosed therein.

Preferred members of this first class of growth hormone secretagogues are 2-amino-N-(2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide, having the following structure:

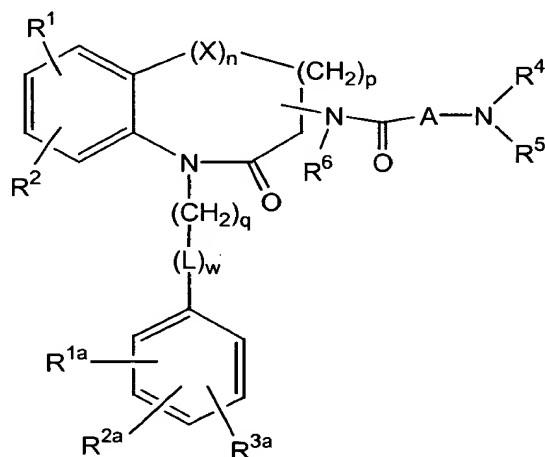


and 2-amino-N-(1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a-(R)-pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, having the following structure:



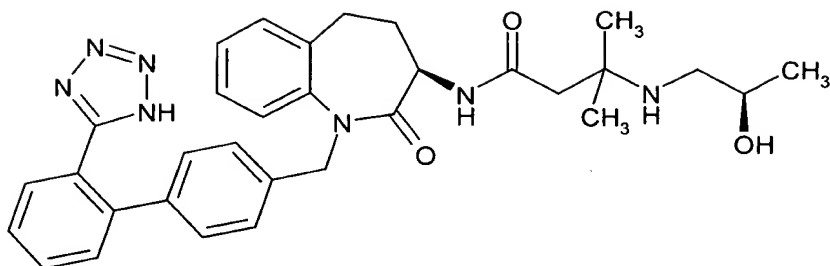
both of which are within the scope of the disclosure of international patent application publication number WO 97/24369. With respect to the latter compound, see also WO 98/58948.

- 5 A representative second class of growth hormone secretagogues is set forth in U.S. patent No., 5,206,235, which is incorporated herein by reference, as having the following structure:

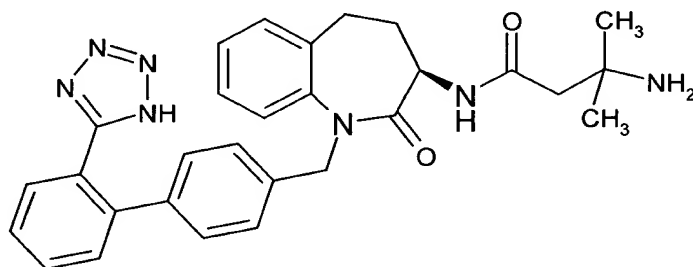


- 10 wherein the various substituents are as defined in U.S. patent 5,206,235. Said compounds are prepared as disclosed therein.

Preferred compounds within this second class include 3-(2(R)-hydroxypropyl)amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide, having the following structure:



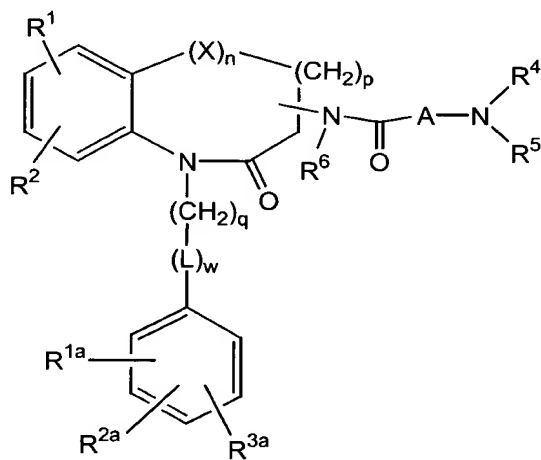
and 3-amino-3-methyl-N-[2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl-1H-1-benzazepin-3(R)-yl]butanamide, having the following structure:



5

both of which are disclosed in U.S. patent 5,206,235.

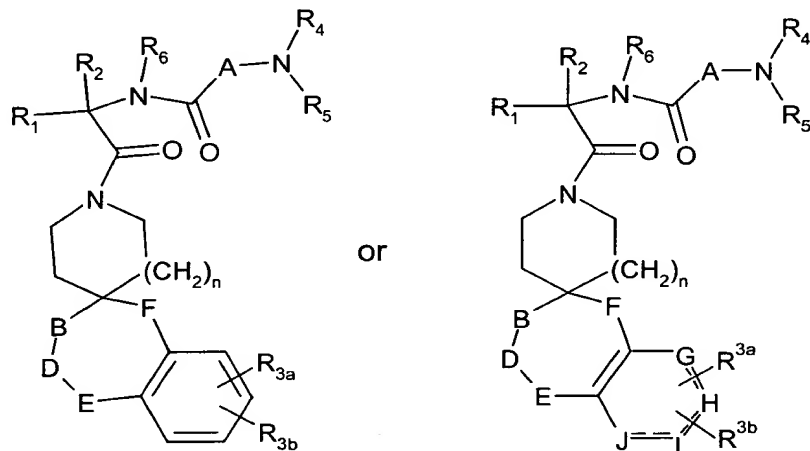
A representative third class of growth hormone secretagogues is set forth in U.S. patent 5,283,241, which is incorporated herein by reference, as having the following formula:



10

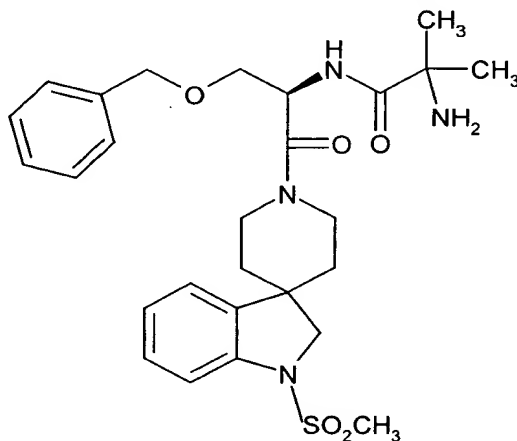
wherein the various substituents are as defined in U.S. patent 5,283,241. Said compounds are prepared as disclosed therein.

A representative fourth class of growth hormone secretagogues is disclosed in PCT publication WO 97/41879, which is incorporated herein by reference, as compounds having the following formulas:



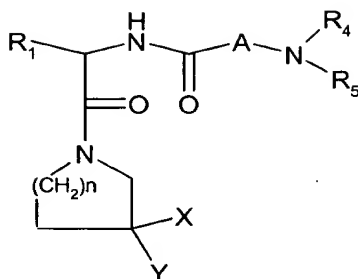
- 5 wherein the various substituents are as defined in WO 97/41879. Said compounds are prepared as disclosed therein.

The most preferred compound within this fourth class which may be employed in the present invention is identified as N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidin]-1'-yl)carbonyl]-2-(phenyl-methoxy)ethyl]-2-amino-2-methylpropanamide, having the following structure:



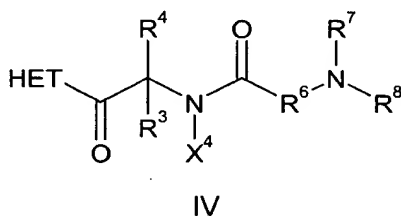
or a pharmaceutically acceptable salt thereof, in particular, the methanesulfonate salt, all of which are disclosed in WO 97/41879.

- 15 A representative fifth class of growth hormone secretagogues is disclosed in U.S. patent 5,492,916, which is incorporated herein by reference, as being compounds of the formula:



wherein the various substituents are as defined in U.S. patent 5,492,916. Said compounds are prepared as disclosed therein.

A representative sixth class of growth hormone secretagogues is set forth in
 5 WO 98/58947, as compounds having the formula:



wherein the various substituents are as defined in WO 98/58947. The preparation of
 the compounds of formula IV of the present invention can be carried out in sequential
 10 or convergent synthetic routes. Syntheses detailing the preparation of the
 compounds of formula IV in a sequential manner are presented in WO 98/58947.

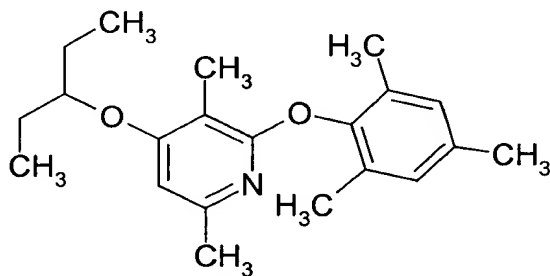
The expression "prodrug" refers to compounds that are drug precursors
 which, following administration, release the drug *in vivo* via some chemical or
 physiological process (e.g., a prodrug on being brought to the physiological pH is
 converted to the desired drug form). A prodrug of any or all of the compounds (i.e., a
 15 CRF antagonist, a growth hormone secretagogue, or a growth hormone) may be
 used in the methods, kits, and compositions of the instant invention. Upon cleavage,
 exemplary prodrugs release the corresponding free acid (where applicable), and such
 hydrolyzable ester-forming residues of the prodrugs of this invention include but are
 20 not limited to carboxylic acid substituents wherein the free hydrogen is replaced by
 (C₁-C₄)alkyl, (C₂-C₁₂)alkanoyloxymethyl, (C₄-C₉)1-(alkanoyloxy)ethyl, 1-methyl-1-
 (alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl
 having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7
 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms,
 25 N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-
 (alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl,

4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)-alkylcarbamoyl-(C₁-C₂)alkyl, piperidino-, pyrrolidino-, or morpholino(C₂-C₃)alkyl, and the like.

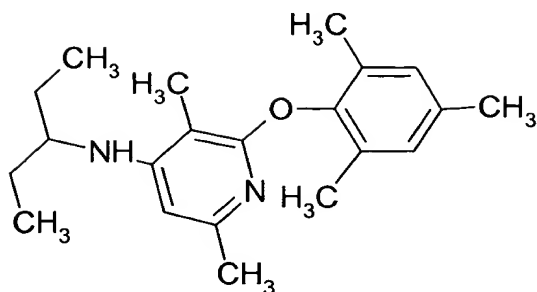
- 5 Other exemplary prodrugs (where applicable) are derivatives of an alcohol of the compounds used in this invention wherein the free hydrogen of a hydroxyl substituent is replaced by (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxy-carbonylamino-methyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanoyl, 10 arylacetyl, α-aminoacyl, α-aminoacyl-α-aminoacyl wherein said α-aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, -P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂, glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate), or the like.

- 15 Of the compositions, methods, and kits of the present invention as defined and claimed herein, particularly preferred are those compositions, methods, and kits that contain one of the following two CRF antagonists:

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine, having the formula

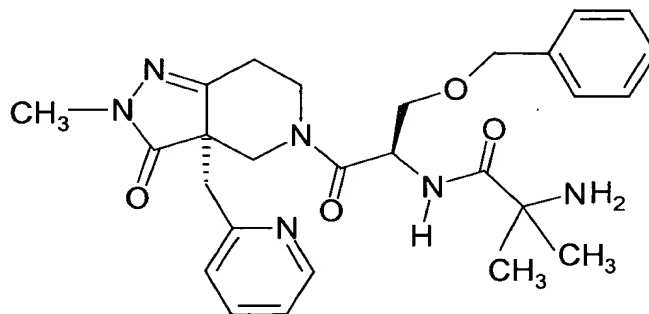


20 or (3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine, having the formula

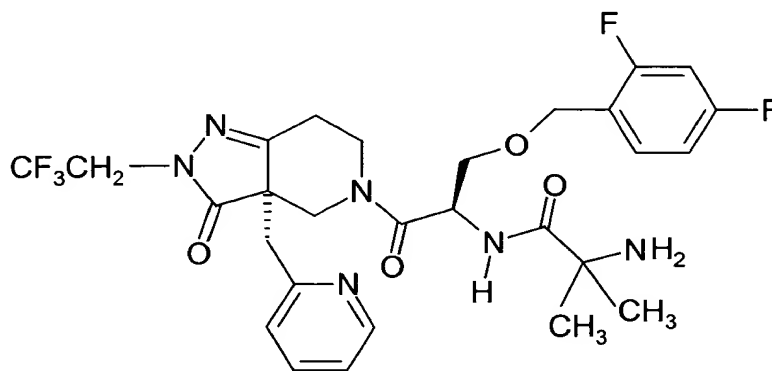


and alternatively one of the following two growth hormone secretagogues:

- 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-
5 c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide, having the formula:



- or 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-(pyridin-2-ylmethyl)-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide, having the formula:



- In the preferred kits of the present invention, the pharmaceutical composition
15 comprising a CRF antagonist is a pharmaceutical composition comprising one of the

preferred CRF antagonists as defined above (i.e., 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine or (3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl)-(1-ethyl-propyl)-amine).

5 In the preferred kits of the present invention, the pharmaceutical composition comprising a growth hormone secretagogue is a pharmaceutical composition comprising one of the preferred growth hormone secretagogues as defined above (i.e., 2-amino-N-[2-(3a(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide or 2-amino-N-(1(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-(3-oxo-3a(R)-(pyridin-2-ylmethyl)-2-10 (2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-ethyl)-2-methyl-propionamide).

In the preferred kits of the present invention comprising both a pharmaceutical composition comprising a CRF antagonist and a pharmaceutical composition comprising a growth hormone secretagogue, the pharmaceutical composition comprising a CRF antagonist comprises a preferred CRF antagonist as defined above and the pharmaceutical composition comprising a growth hormone secretagogue comprises a preferred growth hormone secretagogue as defined herein.

20 The preferred methods of treatment of the present invention are those methods that employ a preferred CRF antagonist, growth hormone secretagogue, or a pharmaceutical composition(s) of the present invention, as defined herein.

Also preferred are those methods that employ a preferred CRF antagonist, growth hormone secretagogue, or a pharmaceutical composition(s) of the present invention, as defined herein, for treating or preventing osteoporosis or frailty associated with aging or obesity, cardiovascular or heart related disease, in particular hypertension, tachycardia, and congestive heart failure, accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or of patients having undergone major surgery.

30 Presently most preferred, the pharmaceutical compositions, methods, and kits of the present invention can be used for treating and preventing congestive heart failure.

Preferably, the combinations of pharmaceutically active compounds of the present invention show a synergistic effect and/or show less side effects, as compared to the individual compounds, when treating a mammal, preferably a human. Thus, in treating or preventing a particular disease, at a specific dosage level, the combinations of the present invention show a better activity than the activity which could be expected when administering the individual compounds and/or show less (or less severe) side effects than could be expected when administering the individual compounds.

The compositions and combinations of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, or subcutaneous injection, or through an implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated with pharmaceutically acceptable carriers, vehicles, or diluents to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, granules, and the like, and for non-human mammals (cats and dogs are the presently preferred non-human mammals) the solid dosage forms can include admixtures with food and chewable forms. In such solid dosage forms, the compounds and combinations of this invention can be admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, starch, or the like. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. In the case of chewable forms, the dosage form may comprise flavoring agents and perfuming agents.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants (such as wetting agents), emulsifying and suspending agents, sweetening agents, flavorings, perfuming agents, and the like.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, emulsions, and the like. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene

glycol, vegetable oils such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories that may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredients in the compositions and methods of this invention may be varied; however, it is necessary that the amount of the active ingredients in such compositions be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, the particular compounds administered, the duration of the treatment, and other factors. All dosage ranges and dosage levels mentioned herein refer to each pharmaceutically active compound present in the pharmaceutical compositions and kits of the present invention, as well as those used in the methods of the present invention. Generally, dosage levels of between 0.0001 to 100 mg/kg of body weight daily are administered to humans and other animals, e.g., mammals.

A preferred dosage range in humans is 0.01 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

A preferred dosage range in mammals other than humans is 0.01 to 10.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A more preferred dosage range in mammals other than humans is 0.1 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The present invention includes within its scope the use of a combination of this invention, e.g., a corticotropin releasing factor antagonist and a growth hormone secretagogue or growth hormone, for the prevention or treatment of congestive heart

failure in mammals. The preferred mammal for purposes of this invention is a human.

Since the present invention has an aspect that relates to treatment with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form.

Thus, in one embodiment, the kit comprises two separate pharmaceutical compositions: a corticotropin releasing factor antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or said prodrug; and a growth hormone secretagogue, a prodrug thereof, or a pharmaceutically acceptable salt of said growth hormone secretagogue or said prodrug. The kit also comprises a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil that is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the

days of the regimen which the dosage form so specified should be ingested. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single
5 tablet or capsule or several tablets or capsules to be taken on a given day. Also, a daily dose of a corticotropin releasing factor antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said corticotropin releasing factor antagonist or said prodrug can consist of one tablet or capsule, while a daily dose of the growth
10 hormone secretagogue, prodrug thereof, or pharmaceutically acceptable salt of said growth hormone secretagogue or said prodrug can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate
15 compliance with the regimen. An example of such a memory-aid is a mechanical counter that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose
20 is to be taken.

In another embodiment, the present invention comprises kits comprising a pharmaceutical composition, a package, and a package insert. The pharmaceutical composition of these kits contains either a corticotropin releasing factor antagonist or a growth hormone/growth hormone secretagogue. The kits of the present invention
25 containing a pharmaceutical composition containing a corticotropin releasing factor antagonist differ from known kits containing a pharmaceutical composition containing a corticotropin releasing factor antagonist in that on the package and/or on the package insert of the kits it is stated that the pharmaceutical composition is to be administered together with a pharmaceutical composition containing a growth
30 hormone or growth hormone secretagogue. The kits of the present invention containing a pharmaceutical composition containing a growth hormone or growth hormone secretagogue differ from known kits containing a pharmaceutical composition containing a growth hormone or growth hormone secretagogue in that on the package and/or on the package insert of the kits it is stated that the

pharmaceutical composition is to be administered together with a pharmaceutical composition containing a corticotropin releasing factor antagonist.

The term "together with" as used in the immediately preceding paragraph is intended to encompass the simultaneous administration of the two pharmaceutical compositions (e.g., a tablet containing one pharmaceutical composition is to be administered orally while the other pharmaceutical composition is administered by way of infusion, two tablets or capsules are to be swallowed together, etc.). The term "together with" is also intended to include the administration of the two pharmaceutical compositions in a specifically timed manner, i.e., one pharmaceutical composition is to be administered a certain time period after administration of the other pharmaceutical composition. The time period in which the two pharmaceutical compositions are to be administered must be sufficiently short for the corticotropin releasing factor antagonist and the growth hormone secretagogue to exhibit their activity contemporaneously, preferably in a synergistic manner. The exact time period depends on the specific compounds of the pharmaceutical compositions, the application route, the kind and severeness of the disease to be treated, the kind, age, and condition of the patient to be treated, etc., and can be determined by a physician using known methods in combination with the disclosure of the present invention. Generally, the two compositions are to be administered within one day, preferably within 5 hours, more preferably within 2 hours, and even more preferably within one hour. Most preferably, the two compositions are to be administered at the same time or one immediately after the other.

Methods that may be used to determine CRF antagonist activity of the compounds employed to practice the present invention are as described in, e.g., Wynn et al., *Endocrinology*, 116:1653-59 (1985), and Grigoriadis et al., *Peptides*, 10:179-88 (1989). Methods that can be used to determine the CRF binding protein inhibiting activity of compounds employed to practice the present invention are described in Smith et al., *Brain Research*, 745(1,2):248-56 (1997). These methods determine the binding affinity of a test compound for a CRF receptor, which is highly related to its expected activity as a CRF antagonist.

The combinations of this invention, i.e., a corticotropin releasing factor antagonist and growth hormone or a growth hormone secretagogue, may be tested for hypoglycemic activity according to the following procedure.

Five to eight week old C57 BL/6J-ob/ob mice (obtained from Jackson Laboratory, Bar Harbor, Maine) are housed five per cage under standard animal care practices. After a one week acclimation period, the animals are weighed and 25 microliters of blood are collected via an ocular bleed prior to any treatment. The
5 blood sample is immediately diluted 1:5 with saline containing 2% sodium heparin, and held on ice for glucose analysis. Animals are then regrouped, in groups of five per cage, such that the mean glucose values of the groups are similar, dosed daily for five days with test compounds (0.01-100 mg/kg), a positive control such as englitazone or ciglitazone (50 mg/kg p.o.), (U.S. Patent 4,467,902; Sohda et al.,
10 *Chem. Pharm. Bull.*, 32:4460-65 (1984)), or vehicle. All compounds are administered by oral gavage in a vehicle consisting of 0.25% w/v methyl cellulose. On day 5, the animals are weighed again and bled (via the ocular route) for blood glucose level determinations. The freshly collected samples are centrifuged for two minutes at 10,000 x g at room temperature. The supernatant is analyzed for glucose, for
15 example, by the ABA 200 Bichromatic Analyzer^{TM1}, using the A-gentTM glucose UV reagent system² (hexokinase method) using 20, 60 and 100 mg/dl standards. Plasma glucose is then calculated by the equation,

20 Plasma glucose (mg/dl) = Sample value x 5 x 1.67 = Sample value x 8.35, where 5 is the dilution factor and 1.67 is the plasma hematocrit adjustment (assuming the hematocrit is 40%).

The animals dosed with vehicle maintain substantially unchanged hyperglycemic glucose levels (e.g., 250 mg/dl), while positive control animals have depressed glucose levels (e.g., 130 mg/dl). The glucose lowering activity of test
25 compounds is expressed in terms of % glucose normalization. For example, a glucose level that is the same as the positive control is expressed as 100%.

¹ TMA registered trademark of Abbott Laboratories, Diagnostics Division, 820 Mission Street, So. Pasadena, CA 91030.

² A modification of the method of Richterrich et al., *Schweizerische Medizinische Wochenschrift*, 101:860 (1971).